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The Influence of Cytoreductive Surgery on the Response to Chemotherapy of a Rat Renal Cancer

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Summary. The potential ability of cytoreductive surgery to increase the effectiveness of chemotherapy (vindesine) was tested utilizing male Wistar Lewis rats transplanted simultaneously with intraperitoneal and flank implants of a spontaneously arising renal adenocarcinoma. Cytoreduction was accomplished in some animals by removing the flank tumor 5–7 weeks following implantation; all animals received vindesine (IP injection of 0.5 mg/kg on two successive weeks). While vindesine reduced tumor growth, in no case did the addition of cytoreductive surgery enhance the effect of chemotherapy. The addition of cytoreductive surgery to marginally effective chemotherapy was found to be ineffective or even detrimental.

Key words: Cytoreductive surgery, Chemotherapy, Renal adenocarcinoma, Rats.

Introduction

It is an appealing clinical theory that either chemotherapy or immunotherapy can be rendered more efficient if the tumor bulk against which these agents must operate is reduced. While this theory has been advocated for a number of human tumors [5, 6, 9, 14], the actual value of cytoreductive surgery remains largely unproven. We have carried out a study to determine whether vindesine (VDR), which is known to reduce tumor growth in a spontaneously arising rat renal cancer model [1], might be rendered more effective by the addition of cytoreductive surgery.

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Abbreviations: VDR = vindesine, IP = intraperitoneal

Material and Methods

When 0.06–0.08 g of this renal adenocarcinoma is placed in the subcutaneous tissue of a syngeneic male rat, a flank nodule will be produced [3]. The tumor does not metastasize from its site of implantation. In order to produce a metastatic model, splenectomy is performed and a similarly size tumor placed intraperitoneally. We have previously described how the nodule model and metastatic model are produced [1, 2] and will only summarize the process here.

Male Wistar Lewis rats weighing between 150 and 200 g were anesthetized with ether, splenectomy was performed, and 0.06–0.08 g aliquots tumor were placed subcutaneously in the flank and within the peritoneal cavity. Incisions were closed with metal clips. In one series of 22 animals the flank and intraperitoneal tumors were allowed to grow for seven weeks. The animals were then divided into 3 groups: 6 received 0.5 ml saline intraperitoneally (IP) at weeks 7 and 9; 8 received VDR at weeks 7 and 9 (0.5 mg/kg IP) and 8 animals were debulked by removing the flank tumor at week 7 and received similar doses of VDR at weeks 7 and 9. Animals were sacrificed at week 10, all visible tumor was removed and wet weight recorded.

A second series of 24 animals with flank and intraperitoneal tumors were studied similarly, except that the tumors were allowed to grow for 5 weeks before treatment manipulations. Thereafter, 12 animals received VDR as above at weeks 5 and 7, 8 animals were debulked as above at week 5 and received VDR at weeks 5 and 7, and 4 animals acted as controls. Animals were sacrificed at week 8, all visible tumor was removed and wet weight recorded.

A third series of 46 animals had tumor implants carried out as above, and at week 7 were divided into 5 groups: 12 acted as controls; 8 received VDR as above at weeks 7 and 9; 8 underwent debulking surgery and no subsequent chemotherapy; 8 underwent a sham operation and received VDR as above and the remaining 8 underwent debulking surgery and received similar doses of VDR. The animals remaining alive at week 10 were sacrificed, all visible tumor was removed and the wet weight recorded.

Results

In the first series of animals sacrificed at week 10 (Table 1), the control rats had approximately equal weights of tumor in the flank and peritoneal cavity, totalling 92 g. The VDR-treated animals had a 61% reduction in total tumor weight,

Table 1. Series I experiments[a]: final tumor weight

Tumor weight	Flank (g wet wt.)	IP (g wet wt.)	Total (g wet wt.)
Control (6)	44.8 ± 7.8[c]	46.5 ± 12.4	91.3 ± 10.1
VDR[b] (8)	23.9 ± 6.5	14.4 ± 5.2	35.2 ± 5.9
VDR[b] + Debulking (8)		39.6 ± 8.7	39.6 ± 8.7

[a] Flank and IP Tumor Implant 7 weeks before treatment
[b] VDR (0.5 mg/kg) Wk. 7 and 9, SAC Wk. 10
[c] Mean ± S.E.

Table 2. Series II experiments[a]: final tumor weights

Tumor weight	Flank (g wet wt.)	IP (g wet wt.)	Total (g wet wt.)
Control (4)	52.4 ± 11.8[c]	34.5 ± 22	86.9 ± 20.2
VDR[b] (12)	51.0 ± 9.2	10.9 ± 2.1	61.9 ± 10.0
VDR[b] + Debulking (8)		16.6 ± 4.25	16.6 ± 4.25

[a] Flank and IP Tumor Implant 5 weeks before treatment
[b] VDR (0.5 mg/kg) Wk. 5 and 7, SAC Wk. 8
[c] Mean ± S.E.

Table 3. Series III experiments: animal survival

	7 Wks.	$7^1/2$ Wks.	8 Wks.
Control	12/12	12/12	9/12 (75%)
VDR[a]	8/8	8/8	8/8 (87.5%)
Debulking	8/8	8/8	8/8 (100%)
Sham + VDR[a]	8/8	8/8	3/8 (37.5%)
Debulking + VDR[a]	10/10	10/10	2/10 (20%)

[a] VDR (0.5 mg/kg) Wk. ± Surgery.

a reduction which was approximately equal in both flank and IP tumor masses, while the debulked, VDR-treated animals had a 51% reduction in total tumor weight as compared to the average total control tumor weight. While VDR effected a significant reduction in both flank and IP tumor weights ($p = 0.05$ and $p = 0.25$), the addition of debulking did not cause any further decrease in the total tumor weight (39.6 + 8.7 g vs. 35.2 + 5.9 g). In fact, the combined treatment resulted in IP tumors which were significantly ($p = 0.025$) larger (39.6 + 8.7 g) than those found in animals treated with VDR alone (14.4 + 5.2 g), and these were not significantly smaller than those of the control animals (46.5 + 12.4 g).

In the second series of animals sacrificed at week 8 (Table 2), VDR was less effective in reducing total tumor weight; with VDR alone, only a 29% reductin of total tumor weight occurred. In this series, debulking plus VDR resulted in no decrease (actually an increase) in the weight of the IP tumor as compared to the IP tumor in animals treated with VDR alone (16.6 + 4.25 g vs. 10.9 + 2.1 g).

The third series of experiments was conducted using a donor tumor 6 generations older than that used in the previous experiments. This tumor generation was significantly more aggressive. At $7^1/2$ weeks, 3 days after the animals had been debulked, or underwent sham surgery, and/or received VDR, all animals were alive. But by 8 weeks a number of animals had died (Table 3). None of the deaths were anesthetic-induced, as evidenced by maintenance of 100% survival at $7^1/2$ weeks. Among the animals not given combination treatment, 25% of controls, 12.5% of VDR-treated, and none of the debulked animals had died. In contrast, of those animals receiving VDR and sham operations there was a 62.5% mortality, while VDR and debulking resulted in an 80% mortality. By 10 weeks, survival in all groups was poor, with no statistical differences to be seen between any groups.

Discussion

Cytoreductive surgery has been advocated in the treatment of malignancy in the hope that it may render chemotherapy more effective. In humans, this approach has been recommended for, among others, thyroid [14], testis [5, 9], and ovarian [6] tumors. In patients with metastatic testicular cancer who have minimal lung disease, chemotherapy will cure over 90% of the cases. In similar patients with bulky lung disease, the complete remission rate using the same effective chemotherapeutic agents is reduced to 50% [4]. Thus, the bulk of disease has directly decreased the effectiveness of

these truly active agents. This does not mean that minimally effective chemotherapy such as is available against human renal adenocarcinoma can be made more effective merely by reducing tumor bulk.

The concept that there is a critical tumor volume against which chemotherapy is most effective has been addressed in a number of animal neplasms with differing results [7, 10]. Using the present tumor model we have shown chemotherapy to be more effective when employed against smaller tumor volumes [1–3]. For example, when cyclophosphamide is employed in this tumor system one week after tumor implantation, the tumor is totally eradicated, whereas when this agent is employed after 5 weeks of tumor growth, there is significant reduction of tumor weight, but no instances of tumor eradication [2, 3]. We have shown similar results employing VDR therapy at different intervals after tumor implantation in this model [1, 2]. A possible explanation for this phenomenon may be that a critical tumor burden is reached, resulting in less effective tumor suppression by these agents. If this were the case, there would be a good argument in favor of cytoreductive surgery.

These experiments were constructed to test whether VDR (which has anti-tumor activity against this renal cancer model) would be rendered more effective with adjunctive cytoreductive surgery. In the first series of animals, the addition of a debulking procedure to VDR-treatment did not reduce the total tumor burden (35.2 g in the VDR-treated group vs. 39.6 g in the VDR-treated/debulked group). Debulking in this experiment was actually counterproductive, since the IP tumor growth of the debulked, VDR-treated animals was higher than that of the IP tumor following VDR treatment alone. Furthermore, there was no significant difference in IP tumor weight in controls and animals undergoing VDR/debulking treatment.

Under the theory that there may be a critical tumor mass against which chemotherapy will work, treatment was started at 5 weeks in the second series of experiments. In these studies, even though there was reduction in total tumor weight following debulking/VDR vs. VDR treatment alone, this reduction was probably the result of simply removing a bulky flank nodule.

Because of the apparent deleterious effect of debulking in the first 2 series of experiments, a third series was designed to study the potential adverse influence of anesthesia/surgery on any beneficial effects that might have been gained from debulking. Putative adverse effects of surgery and general anesthesia were represented in both debulked and non-debulked animals receiving VDR. In this experiment, no animal died 3 days after surgery and/or receiving VDR. However, by one week after surgery and/or VDR, a number of animals had died. Survival was highest in those animals not subjected to combination therapy: 75–100% in control, sham operated or debulked animals, while in animals subjected to the combination of surgery and VDR therapy, survival was only 20–37%. These figures suggest the potential lethal effects of the combination of tumor, surgery, and VDR treatment in this tumor model.

In all groups of VDR treated animals, flank tumor growth was greater than IP tumor-growth. This may be a reflection of better blood suply (and, therefore, better tumor concentration of VDR) in the IP tumor. One of the rationales proposed for using debulking surgery is that it may cause an increase in the mitotic activity of the remaining tumor, thus rendering it more susceptible to chemotherapeutic intervention [12]. Since VDR is principally effective in preventing completion of mitosis, it might have been expected that cytoreductive surgery would have enhanced the effectiveness of this agent. However, we did not find such enhancement in this study. That surgical intervention actually facilitates tumor growth has been previously noted in animal studies [11, 13]; Simpson-Herren has speculated that this more rapid growth might render tumors more sensitive to chemotherapy [13]. However, this study suggests no improved chemosensitivity of the remaining tumor. If there were any increase in chemosensitivity, it appeared to have been outweighed by the detrimental effects of surgery/anesthesia. Recently, Lang and co-workers have found that, in some patients with tumors of the testis undergoing debulking surgery, an activation of the remaining tumor was evidenced by an increase in serum tumor markers [8]. From these studies we conclude that addition of debulking surgery did not increase the effectiveness of marginally effective chemotherapy, and where an effect was evident, it was found to be detrimental.

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