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Effect of Interleukin 1, Inflammation, and Surgery on the Incidence of Adhesion Formation and Death after Abdominal Irradiation in Mice[1]

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ABSTRACT

There is clinical evidence that prior surgery and inflammation can increase the risk of the chronic complications of radiotherapy delivered to the pelvic/abdominal region. We have established a murine model to study this interaction using as end points mortality and late gut-associated peritoneal adhesion formation. A single dose of 16 Gy of total abdominal irradiation (TAI) was used. This gave no early deaths (<1 mo) and a relatively low mortality over the period 1 to 6 mo after TAI. The incidence of adhesions, which is the most serious complication 2 to 6 mo after TAI, was also low.

Injection of lipopolysaccharide (50 μg, i.p.) or human recombinant interleukin 1 (IL-1) in doses as low as 100 units prior to TAI greatly enhanced both radiation-induced adhesion formation and death. Prior surgery also increased radiation-induced mortality, so much so that adhesions could not be accurately quantified. The timing of administration of lipopolysaccharide and IL-1 and of surgery relative to TAI was important in determining the outcome. For example, IL-1 enhanced adhesion formation and death if given from 3 days before to 1 day after, but not 4 days or 4 wk after, TAI. If given 20 h or less before TAI, there was a dramatic increase in early mortality 1 to 3 wk later, which was not seen if IL-1 was given at other times. These early deaths were not caused by bone marrow or gut stem cell depletion and may be a result of fluid leakage.

We propose that surgery, bacterial invasion, or other inflammatory signals might act through a common mechanism of stimulating IL-1 production to enhance radiation-induced adhesion formation and the early and late morbidity and mortality associated with abdominal irradiation. If this is the case, blocking IL-1 production might inhibit the development of these late complications.

INTRODUCTION

Therapeutic irradiation delivered to the pelvic or abdominal region is associated with a risk of chronic radiation enteropathy. These late complications occur 6 to 18 mo after radiotherapy, and the more serious cases present with gut perforation, stenosis, or obstruction due to adhesion formation (1–5). Surgical intervention to clear or bypass gut obstruction is associated with high morbidity and mortality (6–9).

The risk of chronic radiation enteropathy increases with dose and field size (4). It is also higher in patients who have had prior surgery. For example, cervical cancer patients were found to have 2.9 times more radiation-induced bowel injuries if prior laparotomy was performed (10). In patients who had been staged transperitoneally, Piver and Barlow (11) considered that, after 45 to 50 Gy, the number of intestinal complications became unacceptably high. Nussbaum *et al.* (12) concluded that "the risk of irradiation injury to the small bowel, bladder, and rectosigmoid was increased by a major operative procedure just prior to radiation."

Another risk factor for radiation-induced enteropathy is the presence of a preexisting inflammatory response (13–19). Because of these non-dose-related clinical risk factors, we hypothesized that certain inflammatory mediators released following surgery or bacterial insult might modulate gut-associated radiation damage. To test this hypothesis we have studied the impact of recombinant interleukin 1, lipopolysaccharide, and other inflammatory mediators as well as surgery upon the late effects of TAI[2] in mice.

In a recent paper, we showed that the pathogenesis of chronic enteropathy following TAI is complex (20). The nature of the lesion that is seen is does and time dependent. In mice receiving 16 Gy of TAI alone, the most serious complications arose 2 to 6 mo after irradiation and were associated with adhesion formation which could cause loops of bowel to be tied together and obstruct the gut lumen. In our experimental system, adhesions after both single and split-doses of radiation correlated well with lethality.

In this paper we report that adhesion formation and death following TAI are enhanced if mice have had prior surgery or a prior inflammatory state. Furthermore, a dramatic effect was achieved with prior injection of the recombinant cytokine IL-1α even in doses as low as 100 units. IL-1 is a key mediator in the body's response to invasion and injury. Its production is stimulated during inflammatory responses, and it mediates in whole or part, directly or indirectly, biological responses such as fever, somnolence, acute phase protein production, and hematological and vascular changes (reviewed in Ref. 21). It can act as a growth factor for certain cells including fibroblasts (22). Like inflammatory stimuli (23, 24), it can accelerate hematopoietic recovery following WBI (25) and 5-fluorouracil treatment (26) and increase survival in mice subjected to lethal irradiation (27, 28). These radioprotective effects of IL-1 administration on bone marrow after WBI contrast with the harmful effects we demonstrate here after TAI.

MATERIALS AND METHODS

Mice. Ten- to 15-wk-old male C3Hf/Sed/Kam mice, bred and maintained in our SPF defined-flora mouse colony, were used in experiments other than those where surgery was performed which used females of the same age.

Irradiation. TAI was administered using a ^{137}Cs γ-ray source (dose rate, 1 Gy/min). Unanesthetized mice were placed in individual Lucite boxes, positioned in a jig that shielded the head, thorax, and legs with four half-value layers of lead, exposing only the abdomen.

Surgery. Laparotomy was performed by making a midline incision 2 cm long in the abdominal wall. Single oophorectomy was performed in one-third of the mice. In one-third the cecum was abraded by rubbing with a tissue until dry (15 strokes), and in the final third, the organs were left undisturbed. The peritoneal wall was sutured, and the skin was clamped closed.

Inflammatory Stimuli. Lipopolysaccharide B from *Escherichia coli* 026:B6 (Difco, MI) was stored in a freeze-dried state until used. All other reagents were stored at −70°C in phosphate buffer. Saline was used as diluent throughout. Human recombinant IL-1α was supplied by Dr. Peter T. Lomedico of Hoffmann-LaRoche, Inc. (Nutley, NJ) to

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[2] The abbreviations used are: TAI, total abdominal radiation; IL-1α, interleukin 1α; IL-1, interleukin 1; WBI, whole-body irradiation; SPF, specific-pathogen-free; TNF-α, tumor necrosis factor α; LPS, lipopolysaccharide.

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whom we are extremely grateful. The protein consists of the carboxy-terminal 154 amino acids and has a specific activity of 10^8 units/mg in our thymocyte costimulation assay (29). Human recombinant TNF-α (Lot NP102) was a kind gift from Dr. Leo Lin, Cetus (Emeryville, CA). It had a specific activity of 1.8×10^7 units/mg in the L-cell cytotoxic assay (29).

Crypt Scoring. For colonic crypt stem cell survival assays, mice were irradiated with 14.5 or 16.0 Gy of TAI. After 5¾ days, the mice were sacrificed, and the regenerated crypt colonies in transverse sections of the descending colon were counted.

For jejunal crypt stem cell survival assays, mice were irradiated with 16.0 Gy of TAI, and the regenerated crypt colonies were counted 3¾ days later in histological sections of jejunum taken 2 cm distal to the ligament of Treitz.

Statistics. Where appropriate, groups were compared by the Student *t* test.

RESULTS

In a preceding paper (20) we showed that adhesion formation was a major late complication of TAI that first manifested itself 2 mo after irradiation. A small percentage of mice died during the course of the experiment, but none died from acute radiation enteropathy (within the first month). Because inflammation is a known clinical risk factor in radiation enteropathy, we decided to investigate the effect of the inflammatory stimulus LPS on adhesion formation and death. Mice were given injections of 50 μg of LPS 4 days before 16 Gy of TAI. Groups were sacrificed at monthly intervals up to 8 mo thereafter and autopsied. Prior injection of LPS increased the incidence of radiation-induced adhesions and decreased survival at all time points studied (Table 1). LPS alone did not cause adhesion formation or death in the absence of radiation. The time interval between administration of LPS and TAI was important (Table 2). Adhesions were most frequent if LPS was given 4 days before TAI. In all cases, the radiation-induced adhesions were moderately severe, involved the large bowel and, in the vast majority, limited bowel mobility. It was impossible to accurately quantify such adhesions to discover any effect of LPS on their severity.

We had previously shown (20) and discussed the finding that mice receiving TAI died in 3 waves. This pattern is shown again in Fig. 1 for mice receiving 16 Gy of TAI only (starting population of 100 mice, 6 separate experiments pooled). LPS treatment (i.p. Day −4) most markedly affected the pattern of deaths within the first 3 mo (pooled data; starting population, 125 mice). Some mice died between 14 and 28 days which was not seen in the controls.

The effect of surgery on radiation-induced deaths and adhesion formation is shown in Table 3. All mice that received surgery alone survived, and only those that had cecal abrasion developed adhesions. We ignored attachment of the omentum to the suture site which was very common in all control groups. There was a dramatic increase in mortality when surgery preceded TAI. Surgery 1 wk before TAI was worst, with no mice surviving. Almost all these animals died early, *i.e.*, within 3 wk of TAI. If surgery was delayed until 4 wk after TAI, there was a decrease in mortality compared to TAI alone, but it should be noted that, in this experiment, there was an unexpectedly high level of morbidity and mortality in the TAI control group. This is probably because female mice were used in this experiment. Males, which were larger, were used in the other experiments, and a smaller percentage of the body would have been irradiated. Because of the high mortality in these experiments, adhesion formation could not be accurately quantified. Where present, *e.g.*, in mice receiving cecal abrasion 4 wk before TAI, there was a more generalized and severe response in the groups receiving surgery and TAI, with multiple dense adhesions present, compared to single site adhesions in the controls.

Because mediators like IL-1 are known to be released during the inflammatory response that follows microbial invasion or surgical injury to the host, we chose to examine the effect of this cytokine on radiation-induced adhesion formation and death. Injection of human recombinant IL-1α without TAI did not cause adhesions or deaths. However, when administered 3 days prior to 16 Gy of TAI, 100% of mice receiving 10^2 or 10^3 units of IL-1α developed severe adhesions (Table 4). Deaths were also increased. When IL-1α was given 1 h before TAI, the majority of mice died early, *i.e.*, within 10 days. This dramatic increase in early mortality was not seen if TNF-α, a cytokine

Table 1 *Effect of LPS upon survival and adhesion formation after 16 Gy of TAI as a function of time*

Treatment	Sacrifice time (mo)	No. of survivors (%)[a]	Incidence of adhesions (%)[b]
TAI alone	1–3	100	7
	4–5	100	10
	6–8	93	43
TAI + 50 μg of LPS, Day −4[c]	1–3	93	43
	4–5	90	67
	6–8	65	85

Groups of 15 mice were given 16 Gy of TAI. The number surviving to 3, 5, or 8 mo is given.
[b] Incidence of adhesions in the survivors at Day 210.
[c] Fifty μg of lipopolysaccharide were injected i.p. 4 days before TAI.

Table 2 *Effect of the timing of LPS administration upon radiation-induced adhesion formation*

Treatment	No. of survivors (%)[a]	Incidence of adhesions (%)[a]
LPS[b] only	100	0
TAI[c] only	96	29
LPS[b] − 8 wk + TAI[c]	60	50
LPS − 6 wk + TAI	80	50
LPS − 4 wk + TAI	80	63
LPS − 2 wk + TAI	89	67
LPS − 1 wk + TAI	100	40
LPS − 4 days + TAI	77	71
LPS − 1 day + TAI	85	29
LPS + 1 day + TAI	100	33
LPS + 4 days + TAI	60	33

[a] Ten to 40 mice/group. Survivors were sacrificed at 188 days after TAI and adhesions scored.
[b] Fifty μg of LPS i.p.
[c] Sixteen Gy of total abdominal irradiation.

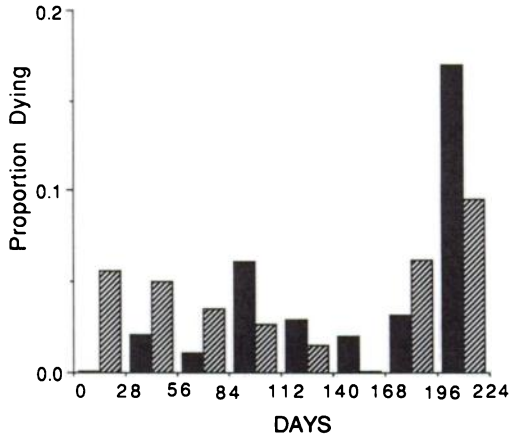

Fig. 1. The proportion of mice dying over 28-day intervals after 16 Gy of TAI (■) or LPS (50 μg i.p.) 4 days before 16 Gy of TAI (■). The starting populations contained 100 and 125 mice, respectively. This represents pooled data from 6 different experiments, each containing LPS-treated mice with matched controls.

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Table 3 *Effect of surgery on survival and adhesion formation following 16 Gy of TAI*

Time of surgery relative to TAI	Laparotomy		Oophorectomy		Cecal Abrasion	
	% survival[a]	% adhesions[b]	% survival	% adhesions	% survival	% adhesions
−4 wk	0		20	50	50	80
−1 wk	0		0		0	
+1 wk	0		40	100	24	75
+4 wk	70	86	78	75	67	50
Surgery alone	100	0	100	10	100	80
TAI alone	40	75				

[a] Nine or 10 female mice per group.
[b] Survivors sacrificed 126 days after 16 Gy of TAI and adhesion incidence measured.

Table 4 *Effect of IL-1α and TNF on survival and on adhesion formation after 16 GY of TAI*

Treatment	No. surviving (%)[a]	Median time to death (days)[a]	Incidence of adhesions (%)[b]
IL-1α, 10^4 units alone	100		0
TAI + saline i.p., −1 h[c]	70[a]	80	21.4
TAI + IL-1α, 10^1 units, −1 h	60	40	16.6
TAI + IL-1α, 10^2 units, −1 h	50	9	30.0
TAI + IL-1α, 10^3 units, −1 h	30	8	33.3
TAI + IL-1α, 10^4 units, −1 h	30	8	66.6
TAI + IL-1α, 10^1 units, −3 days[c]	80	116	25.0
TAI + IL-1α 10^2 units, −3 days[c]	60	80	100.0
TAI + IL-1α, 10^3 units, −3 days[c]	40	56	100.0
TAI + IL-1α, 5×10^3 units, −3 days[c]	50	108	40.0
TAI + IL-1α, 10^3 units, +4 wk	90	88	0
TAI + TNF, 10^2 units, −1 h	60	47	16.6
TAI + TNF, 10^3 units, −1 h	50	42	0
TAI + TNF, 10^4 units, −1 h	70	65	28.5

[a] Groups of 10 to 20 mice received 16 Gy of TAI and the stated treatments. The number surviving (%) on Day 133 and the median time to death are shown.
[b] The incidence of adhesions in surviving mice 133 days after irradiation.
[c] All interleukins were given i.p. in 0.2-ml volumes of saline diluent at the stated times.

Table 5 *Effect of timing of IL-1α administration on survival and adhesion formation after 16 TAI*

Treatment	No. surviving (%)	Median time to death (days)[a]	Incidence of adhesions (%)[b]
TAI + saline i.p., −1 h[c]	70	54	57.1
TAI + IL-1α, −3 days[c]	60	53	83.3
TAI + IL-1α, −20 h	30	15	66.7
TAI + IL-1α, −4 h	10	8	100
TAI + IL-1α, +4 h	70	41	85.7
TAI + IL-1α, +1 day	30	54	100
TAI + IL-1α, +4 days	90	54	33.3

[a] Groups of 10 mice received 16 Gy of TAI and the stated treatments. The number surviving (%) on Day 88 is shown along with the median time to death.
[b] The incidence of adhesions in the survivors 88 days after irradiation.
[c] IL-1α (10^3 units) was given i.p. in 0.2-ml volumes of saline diluent at the stated times.

Table 6 *Effect of IL-1α on peripheral WBC levels 3 days after TAI*

	Peripheral WBC count ($\times 10^6$ ml)		
	Saline	IL-1α, −3 days[a]	IL-1α, −3 h[a]
No TAI	9.4 ± 0.65[b]	7.9 ± 0.21	8.6 ± 0.97
16 Gy of TAI	1.6 ± 0.21[c]	3.1 ± 0.07[c, d]	1.0 ± 0.23[d]

[a] IL-1α (10^3 units) given i.p. to mice in a volume of 0.2 ml in saline diluent either 3 days or 3 h before TAI or no TAI.
[b] Mean ± SE.
[c] $P < 0.001$ compared to nonirradiated controls.
[d] $P < 0.001$ compared to 16 Gy-irradiated controls.

Table 7 *Effect of IL-1α on colonic and jejunal crypt survival after TAI*

	Crypt count after TAI		
	0 Gy	14.5 Gy	16.0 Gy
Colon[a]			
TAI only	153.2 ± 3.9[b]	96.2 ± 3.5	71.6 ± 2.3
TAI + IL-1α,[c] −3 days	151.8 ± 5.1	102.0 ± 2.9	66.0 ± 4.0
TAI + IL-1α,[c] −3 h	141.4 ± 4.5	92.3 ± 3.8	61.0 ± 2.7
Jejunum[d]			
TAI only	158.2 ± 2.9	ND[e]	12.6 ± 0.6
TAI + IL-1α,[b] −3 days	156.6 ± 0.4	ND	11.4 ± 0.9
TAI + IL-1α, −1 h	ND	ND	13.0 ± 0.8

[a] Human recombinant IL-1α i.p. (10^3 units).
[b] Mean ± SE.
[c] Crypts surviving after 5¾ days (colon).
[d] Crypts surviving after 3¾ days (jejunum).
[e] ND, not done.

whose production is stimulated by IL-1, was injected just prior to TAI. The timing of this phenomenon was investigated further. Early deaths were seen in mice given IL-1α within the 20 h preceding TAI (Table 5) but not 3 days before TAI or at any time after TAI. IL-1 did, however, enhance adhesion formation if given from 3 days before up to 1 day after TAI, but not 4 days or 4 wk after TAI.

We have investigated several possible reasons for the early deaths in mice receiving IL-1α just before 16 Gy of TAI. IL-1α is known to protect against bone marrow death in total-body irradiated mice and to stimulate hematopoiesis following irradiation, making bone marrow depletion an unlikely cause. This view is supported by our finding that, while TAI dramatically reduces the whole blood cell count measured 3 days later, IL-1α 3 h prior to TAI had no deleterious effect and if given 3 days earlier was protective (Table 6). Because a role for endotoxin in acute hemorrhagic enteropathy has been suggested (30), we studied the effect of IL-1 and TAI on gut histology, combining it with colon and jejunal crypt counts as a measure of stem cell survival. IL-1α did not affect colonic or jejunal (Table 7) stem cell survival, and there were no obvious histological differences between the IL-1-treated and control groups at this time period. Histological examination of jejunum and colon from mice killed 88 and 133 days after TAI showed serosal breakdown and lymphoid hyperplasia in animals with adhesions and mild vascular damage and fibrosis as generalized findings (20). IL-1 treatment did not qualitatively alter the histopathology, only its incidence.

DISCUSSION

In an earlier paper, we showed that, although the pathogenesis of radiation enteropathy is complex and several mechanisms can precipitate morbidity and mortality, adhesion formation involving the large bowel seems to be a major complication 2 to 6 mo following 16 Gy of TAI of mice (20). The adhesions that follow irradiation are slow to form and dense and do not readily resolve. There is a close correlation between single and split-dose radiation responses of adhesion formation and death following TAI of mice.

The most striking finding presented in this paper is that very low doses of IL-1α injected i.p. prior to TAI dramatically increase adhesion formation and deaths. IL-1 is a cytokine produced by the host during the inflammatory response follow-

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ing microbial invasion or physical injury. We suggest that it could form a common pathway by which inflammation and surgery could act to increase the risk of radiation enteropathy. These are both known clinical risk factors. It is of interest that diabetes mellitus is also a clinical risk factor, that IL-1 has been shown to be a potent inducer of insulin transcription, and that overstimulation of β-islet cells by IL-1 causes their death (21). While diabetes is an obviously complex disease state, IL-1 may prove to be a link between it and enhanced risk of radiation enteropathy.

IL-1 is not made constitutively by many cells, but its production can be induced in a wide variety of cells including fibroblasts, keratinocytes, kidney mesangial cells, vascular endothelium, smooth muscle cells, and certain lymphoid, brain, and epithelial cells. The stimuli for its production include bacterial products, T-cell products, and injury (see Ref. 21). The most efficient producers of large quantities of IL-1 are stimulated macrophages which are plentiful in the peritoneal cavity and the gut-associated lymphoid tissues and which could easily produce the levels of IL-1 shown to be effective in this study (21, 31).

The mechanisms of action of IL-1 and LPS in enhancing radiation-induced adhesion formation and death require elucidation. IL-1 and LPS have a myriad of effects *in vivo*. Those of seeming relevance to this study include mediating vascular endothelial inflammatory changes (32, 33) regulating fibrin deposition and lysis (32, 34–37), increasing collagenase production by fibroblasts and collagen type IV deposition by epithelial cells (38), stimulating fibroblast proliferation (22), and modulating hematopoiesis and granulopoiesis (24–28, 39).

It is relevant to note that early deaths occurred in some groups of animals, notably those receiving IL-1 20 h and less before TAI, those that were operated on 1 wk before TAI, and a small percentage of those given LPS and TAI. None of the controls died at this time (up to 28 days). Obviously these deaths were not due to adhesions. Bone marrow death can be ruled out at least for IL-1 and LPS, and there was no evidence that crypt histology or crypt stem cell survival was affected. The most appealing explanation is that they died as a result of leakage of fluid through a disturbed vasculature or serosal surface and IL-1 and radiation interact in causing this to happen.

This hypothesis might also explain why late adhesion formation can be enhanced in mice that survive this early phase. LPS and IL-1 are known to have direct effects on endothelial cells (21, 32, 33), and IL-1 can move endothelial cells in the direction of maintaining and generating fibrin (34). Endothelial damage caused directly or indirectly through IL-1/LPS-induced leukocyte activation and adhesion to endothelium could lead to leakage and could contribute to or act synergistically with similar early radiation-induced changes. A similar scenario might take place at the serosal surface where histological examination suggests that IL-1 administration makes more severe the serosal breakdown seen in mice receiving TAI (20). Also associated with radiation-induced adhesion formation is hyperplasia of the gut-associated lymphoid tissue (20). Although it is not known whether there is a cause or effect relationship, it seems possible that IL-1 could stimulate local immune responses which may indirectly contribute to the pathology.

It is of interest that TNF-α which shares with IL-1 some, but not all (32), biological functions did not have the same effects of mortality or adhesion formation. Further investigation of the spectrum of active and inactive cytokines on their own or in combination (26, 28, 32) may give us a better indication of the causative mechanisms under investigation.

The question arises as to whether IL-1 has a natural role in radiation enteropathy. It is clear that an insult prior to TAI has a more dramatic effect than after TAI, and therefore cytokine production in response to irradiation (40) alone or as a result of leakage of bacterial components from the damaged gut (1, 30, 41, 42) is likely to be most relevant during a fractionated course of radiation. The role of the bacterial gut flora in radiation mortality and gut pathology has long been discussed (30, 41, 43–50), largely from the point of view of infection, but it is still uncertain whether clinically relevant doses of radiation would cause sufficient leakage of gut contents to alter biological responses. It should be noted that our mice are specific pathogen free and that conventional mice, and probably humans, have considerably more complications following TAI, including a lower 50% lethal dose.[3]

Corticosteroids and certain lipoxygenase inhibitors are known to block IL-1 transcription and decrease its production (51, 52). It would be of interest to see if these affect radiation-induced enteropathy. Trott *et al.* (18) have shown that antibiotics and local corticosteroids together, but not alone, enhanced survival of rats receiving local rectosigmoid irradiation. In this study the rats died largely of rectal obstruction caused by ulceration.

Finally, it is clear that both LPS and IL-1, which are known protectors of bone marrow following total-body irradiation, can sensitize mice to both the early and late effects of total abdominal irradiation, and that these agents are therefore best considered to be radiation response modifiers rather than radioprotectors.

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