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REVIEW PAPER

Advances in Mitigation of Injuries from Radiological Terrorism or Nuclear Accidents

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ABSTRACT

A program to deal with the medical consequences of a radiological terrorism incident or a nuclear accident requires three principal components: (i) the technology to rapidly determine the radiation doses received by a large number of people, (ii) methods for alleviating acute hematological radiation injuries, and (iii) approved drugs for mitigation of chronic radiation injuries. Laboratory studies have shown that all these needs can be met theoretically. However, moving from the existing laboratory studies to a deployed program is not easy. The work that still needs to be done is expensive and time-consuming, and the move from the laboratory to the field may also face severe regulatory barriers.

Keywords: Radiological terrorism, nuclear accident, countermeasures, biodosimetry, acute radiation syndrome

1. INTRODUCTION

The United States and India have become strategic partners for developing peaceful uses of nuclear energy[1], but both countries are vulnerable to radiological terrorism or nuclear accidents. Soon after the 11 September 2001 attacks on the World Trade Centre and the Pentagon, scientists in the United States began to question the country's ability to cope with a radiological terrorism incidents[2]. The outline of what was needed was fairly obvious: (i) the ability to prevent such an attack;(ii) methods to cope with the medical consequences; (iii) the ability to clean up afterwards; and (iv) the tools to figure out who did it[3] (Fig. 1).

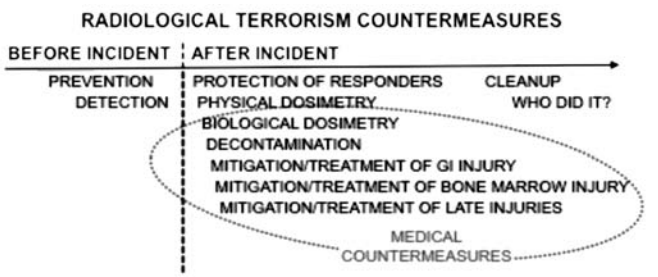

Figure 1. The components of a complete radiological terrorism countermeasures programme. (Adapted with permission from Moulder[3]).

In the United States, centres for countermeasures against radiation were established for rapid development of biodosimetry, decorporation agents, and medical countermeasures[4]. In India, nuclear research and development was pioneered by the first Prime Minister Pundit Jawaharlal Nehru with the help of Dr Homi Bhabha and other leading scientists. Their initiatives resulted in the building of prominent research institutes where radioprotectors and countermeasures against ionizing radiation from indigenous herbs are being developed[5]. This review focuses of the current status of the medical components needed to cope with a mass-casualty radiological or nuclear incident: rapid biodosimetry, therapies for acute radiation syndrome (ARS), and therapies for late injuries.

2. WHY WORRY ABOUT ORGAN SYSTEMS OTHER THAN BONE MARROW?

In the Chernobyl accident, the acute 50 per cent lethal dose (LD_{50}) was about 6 Gy[6]. If a similar-size incident were to occur now, advances in treatment of ARS are such that there would probably be survivors with exposures[2] as high as 8-12 Gy (Fig. 2). Upper-body doses as high as this would cause radiation pneumonitis[7] (Fig. 2), and might also cause cognitive impairment[8,9] and cardiac injury[10,11]. Lower-body doses as high as this would result in severe prodromal emesis and diarrohea[12,13] (Fig. 2) and would exceed renal tolerance[14,15] (Fig. 2). Thus, an effective medical counter-measures program needs to deal with both acute hematological injury, and with delayed injury to organ systems as diverse as kidney, lung, heart and brain[2].

3. PROTECTION VERSUS MITIGATION VERSUS TREATMENT

The term "radioprotector" has long been used in radiobiology to refer to prophylactic agents that must be given before radiation exposure; mitigators are agents that are given after radiation exposure, but before the appearance of overt evidence of injury; and treatment refers to thoseagents that are given after overt symptoms develop[16] (Fig. 3).

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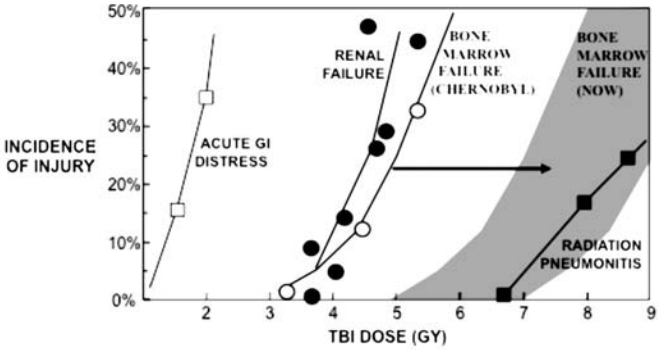

Figure 2. The relationship between total body irradiation (TBI) dose and toxicity. Dose-response data are shown for hematopoietic lethality after the Chernobyl accident (○)[6] and for how that lethality dose-response curve might look if a similar incident happened now (gray area). Data are also shown for acute radiation-induced nausea and vomiting (□)[13], chronic renal failure (●)[14], and pneumonitis (■)[7]. (Adapted with permission from Moulder[3]).

Figure 3. Recommended terminology for therapeutic approaches to radiation-induced normal tissue injuries. (Adapted with permission from Stone[16], *et al.*)

All three approaches have been assessed in clinical or preclinical studies. Prophylactic agents include free radical scavengers[17,18] and herbal radioprotectors[19,20]. Mitigators include suppressors of the renin-angiotensin system[21-23] and suppressors of chronic oxidative stress[23-25]. Treatment agents include some of the drugs that are effective as mitigators[22,24], but also include agents such as pentoxifylline to treat radiation fibrosis[26,27] and growth factors to facilitate recovery from hematological injury[28,29]. In India, a wide range of herbal and nutriceutical countermeasures are being developed[20,30] as clinical models[31] for testing novel agents.

4. COMPONENTS OF A MEDICAL COUNTERMEASURES PROGRAMME

In dealing with the medical consequences of radiological terrorism or nuclear accidents, there are three major biomedical issues: (i) determining exposure, (ii)dealing with acute radiation injuries, and (iii) dealing with chronic radiation injuries[32,33]. Biodosimetry is of little practical use unless there are effective therapies. Therapies for acute injuries will have very few long-term benefits unless there are therapies for the late effects that will occur in people who receive high doses and for whom hematological toxicity cannot be presented (Fig. 2). Conversely, therapy for chronic radiation injuries will be of little use without development of better biodosimetry tools, and better methods for decreasing acute hematological toxicity.

5. PROGRESS ON BIODOSIMETRY

The need for medical intervention requires knowing radiation doses, preferably organ-specific doses[33-35]. While there are sophisticated and widely available instruments for assessing contamination, the available tools for retroactive assessment of radiation doses are either primitive or are not widely available[33,36,37]. If a mass-casualty incident occurs now, the only method for rapid (<12 h) radiation dose assessment would be "time to emesis"[37]. This is not actually very useful, since not all irradiated people (even those with large abdominal doses) vomit, and in many mass casualty scenarios, there will be other reasons that will cause people to vomit[36,38].

If more time was available, dose estimates could be made based on lymphocyte depletion kinetics, but that takes at least a day[36,37]. In theory, doses could also be based on chromosome aberrations in blood lymphocytes, but this assay takes days and requires samples to be sent to central laboratories whose capacity is limited[33,36,37].

Recent research has shown that faster and more deployable systems are theoretically possible. Dr Harold Swartz's group at Dartmouth Medical School (Hanover, New Hampshire, USA) has developed portable electron paramagnetic resonance (EPR) dosimeters that can measure low-LET radiation doses from teeth and finger nails[39,40]. The EPR signal is durable and it appears that the techniques can detect doses as low as 2 Gy[36,39,40]. Dr David Brenner's group at Columbia University Medical Centre (New York, USA) has taken a very different approach, and is developing an automated device for measuring radiation-induced micronuclei and δ-H2AX fluorescence in blood lymphocytes[41]. However, machines such as these will not be deployed anytime soon, as currently there is no market to support the cost of manufacturing the units and/or the cost of getting these approved by the required authorities (*e.g.*, in the USA, by the Food and Drug Administration).

6. PROGRESS ON MITIGATION OF ACUTE RADIATION SYNDROME (ARS)

A number of groups have devoted considerable effort to improving treatment of ARS[29,42-44]. Interestingly, high-quality supportive care may be far more important than any of the new biologicals or pharmaceuticals. For example, Dr George Georges's group at the Fred Hutchinson Cancer Research Centre (Seattle, Washington, USA) has shown that the canine LD_{50} can be increased from <4 Gy to about 8 Gy by providing human-standard supportive care (e.g., isolation, hydration, antibiotics, transfusions). Adding state-of-the-art cytokine therapy to this supportive care did not further[45] increase the LD_{50}.

After a radiation terrorism incident with doses > 4 Gy, providing supportive care to a large number of victims will be the immediate challenge. This challenge becomes more severe by the fact that it is not clear which aspects of supportive care are most important. Dissecting supportive care to find out what really matters will be difficult, as

the studies needed are considered problematic by many of the authorities that regulate animal studies (e.g., in the USA, by the Institutional Animal Care and Use Committees).

7. PROGRESS ON MITIGATION OF LATE NORMAL TISSUE INJURY

In the laboratory, a wide range of late normal tissue injuries can be mitigated using therapies that are not started until days to weeks after irradiation[25,46-54]. Such mitigation was first demonstrated in models of renal injury using angiotensin-converting enzyme inhibitors (ACEi's) that are commonly used in human beings to treat hypertension and heart disease[46]. Subsequently, the ACEi's were also shown to mitigate experimental radiation-induced lung[47], brain[48], and cardiac[49] injuries. One of the ACEi's, captopril, has now made the leap from bench-to-bedside and has been shown to be effective for mitigation of radiation-induced renal injury in human beings[50] (Fig. 4). A related type of antihypertensive drug, the angiotensin II type-1 receptor blockers, are also effective for mitigation of some types of radiation injuries[46], but other types of anti-hypertensive agents are not[51].

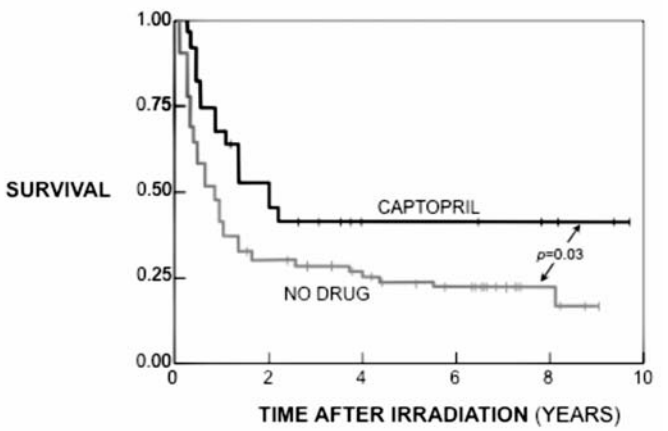

Figure 4. Actuarial patient survival in a clinical trial using captopril, an ACEi, to mitigate chronic renal failure in subjects undergoing TBI-based hematopoietic stem cell transplant (Adapted with permission from Lawton[15], *et al.*).

A second class of agents that has shown promise for mitigation of late radiation injuries are the superoxide and catalase mimetics[25,52-54]. Unfortunately, the superoxide/catalase mimetics that show promise as radiation mitigators in laboratory studies are not yet approved for human use.

To make these mitigators available for use after a radiological terrorism incident will not be easy, at least not in the USA. Current regulations in the USA require that in order for agents to be readily available for use after a radiological terrorism incident, they must not only be approved for human use, but they must be specifically labeled for use as radiation counter measures. Even use of a drug to mitigate radiation injuries in cancer patients (e.g., captopril[50]) is not considered by regulators in the USA to be a proof that it is suitable for use as a radiological terrorism countermeasure. Since people cannot be irradiated to test whether candidate mitigators are effective, their efficacy will need to be proven using animal studies[31,55]. To our knowledge, this route to drug labeling has never been tried for a radiation mitigator and it is not clear that the required studies are even feasible; but at a minimum, satisfying the regulations will require time- and money-intensive efforts. How India or other countries will handle this issue is not yet clear.

8. WHAT IF AN INCIDENT HAPPENED NOW?

The good news from the laboratory is that they now have "proof of principle" that an effective medical countermeasures programme is possible: methods for rapid large-volume biodosimetry could be developed and deployed; the acute effects of radiation can be alleviated; the chronic effects of radiation on normal tissues can be mitigated.

The bad news is that moving from laboratory studies to a deployed programme will not be easy. The work that still needs to be done is expensive and time-consuming, and the move from the laboratory to the field may face severe regulatory barriers.

The best current role for the radiation safety and defence community is to use their resources and expertise to make sure that radiological terrorism and nuclear accidents do not occur. But all potential first responders should also have a emergency response database such as REMM Radiation Emergency Medical Management http://www.remm.nlm.gov) loaded on their computers.

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