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Cancer Events After Acute or Chronic Exposure to Sulfur Mustard: A Review of the Literature

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ABSTRACT

Background: Sulfur mustard (SM) has been considered as a carcinogen in the laboratory studies. However, its carcinogenic effects on human beings were not well discussed. The main purpose of our study is to assess carcinogenesis of SM following acute and/or chronic exposures in human beings.

Methods: The valid scientific English and Persian databases including PubMed, Web of Science, Scopus, IranMedex, and Irandoc were searched and the collected papers reviewed. The used keywords were in two languages: English and Persian. The inclusion criteria were the published original articles indexed in above-mentioned databases. Eleven full-texts out of 296 articles were found relevant and then assessed.

Results: Studies on the workers of the SM factories during the World Wars showed that the long-term chronic exposure to mustards can cause a variety of cancers in the organs such as oral cavity, larynx, lung, and skin. Respiratory system was the most important affected system. Acute single exposure to SM was assumed as the carcinogenic inducer in the lung and blood and for few cancers including basal cell carcinoma and squamous cell carcinoma.

Conclusions: SM is a proven carcinogen in chronic situations although data are not enough to strongly conclude in acute exposure.

Keywords: Cancer, chemical warfare, Iraq-Iran war, mustard gas, sulfur mustard

INTRODUCTION

During the Iraq-Iran war (1980–1988), the Iranian troops and some ordinary people were attacked 387 times,[1] by more than 1800 tons of sulfur mustard (SM) gas by the Iraqi armies. Consequently, over 100,000 military or civilian people were exposed to SM,[2] and thus a considerable proportion of exposed people are still suffering from the long-term consequences of exposure such as respiratory, ocular, and dermatology problems.[3-6] As well, SM was used as a chemical weapon by the Iraqi armies against indigenous Iraqi Kurds.[7-9]

The carcinogenic effect of SM has already been evaluated in laboratory and human being studies.[10,11] SM is a

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nucleophilic and lipophilic agent and due to this property, it can diffuse through the body and can change DNA structure. These DNA changes are involved in producing acute toxicity as well as long-term carcinogenicity of SM.[12]

Alkylation reaction disrupts DNA replication and protein synthesis by replacing hydrogen by an alkyl group which is the equivalent of an alkyl anion (carbanion).[13,14] The changes created by SM in the DNA base explain the mutagenic and carcinogenic of SM.[15]

According to the International Agency for Research on Cancer report in 1975, SM is a well-known carcinogen in animals and human.[16]

Although SM has been considered as a carcinogen in the laboratory studies, its carcinogenic effects, particularly on acute situations, have not been well discussed yet. The aim of this study was to review the published articles discussing on human cancers in relation to SM acute and/or chronic exposures.

METHODS

During a systematic search, we used PubMed, Scopus, Web of Science, Iranmedex, and Irandoc to evaluate the international and national medical databases. Two hundred and ninety-six records were extracted, and their contents were subsequently reviewed. The used keywords were in English and Persian languages. The inclusion criteria were published the original articles in valued journals indexed in the above-mentioned databases. The exclusion criteria were animal studies. All of the original papers which studied acute or chronic carcinogenic consequences of SM were included. There was no time interval limitation for searching databases. Most of the studies had focused on respiratory, dermatological, and ophthalmological complications. After title and abstract screening, 11 articles were found relevant to the aim of this study and their full-texts were subsequently evaluated. The study was carried out in accordance with the principles of the Ethics Review Board of Tehran University of Medical Sciences.

RESULTS

Chronic exposure

The studies which considered the associations between various cancers and occupational chronic exposure of mustard gas are summarized in Table 1.

Oral cavity

There was an increased mortality resulted from oral cavity cancers in the workers who had chronic exposure to mustard gas. Easton *et al*., in a cohort study, conducted on 2498 men and 1032 women, found a strong relationship between exposure to SM and cancers of the lip, tongue, salivary glands, and mouth.[18] The association between laryngeal and tracheal cancers was reported by Manning *et al*. among SM factory workers (1939–1945).[19]

Lung cancers

Doi *et al*. compared 480 exposed with 969 unexposed workers in an SM factory in Japan from 1929 to 1945. They concluded that the workers were at risk of developing lung cancer.[15] As well, mortality of lung cancer in exposed workers significantly increased in comparison to unexposed ones.[17] Moreover, Easton *et al*. in their study found a strong relationship between SM exposure and lung cancer.[18]

Skin cancers

Bowen's carcinoma (squamous cell carcinoma *in situ*) was reported due to occupational exposure to mustard gas by Inada *et al*.[20]

Acute exposure

The studies which evaluated the relationship between acute SM exposure and various cancers are summarized in Table 2.

Zafarghandi *et al*. conducted a cohort study and compared the incidence rates of malignancies in 7570 veterans who exposed to SM and 7595 unexposed people in a 25-year follow-up period.[10] Although they found an increased age-specific incidence rate of cancer in the exposed rather than unexposed population, no evidence of increased age-adjusted incidence rate of specific cancer types was found.

Table 1: The results of some studies evaluated the carcinogenicity of sulfur mustard in occupational condition among sulfur mustard factory workers

Reference	First author	Involved organ	Year of study	Elapsed times after exposure (years)	Duration of exposure	Place	Population/number	Carcinogenicity of SM
[15]	Doi	Lung	2011	16	1929-1945	Japan	480 exposed and 969 unexposed workers	+
[17]	Wada	Airways cancers	1968	16	1929-1945	Japan	33 deaths	+
[18]	Easton	Respiratory tract	1988	43	Long-term	England	3530 men and women	+
[19]	Manning	Larynx and trachea	1981	6	1939-1945	England	511 men and women	+
[20]	Inada	Multiple Bowen's disease	1978	3-46	Long-term	Japan	5 workers	+

SM=Sulfur mustard

Table 2: The results of some studies evaluated the carcinogenicity of sulfur mustard in Iranian veterans after Iraq-Iran war

Reference	First author	Type of cancer	Year of study	Time after exposure (years)	Duration of exposure	Place of study	Population/number	Carcinogenicity of SM
[10]	Zafarghandi	Various malignancies	2013	25	Short	Sardasht city	7570 veterans exposed to SM and 7595 unexposed people	+
[7]	Hosseini-khalili	Lung	2009	5-20	Short	Tehran city	20 veterans	+
[21]	Zakeri Nia	Different hematologic malignancies	2002	>15	Short	Fars province	3000 veterans	+
[22]	Ghanei	Chronic myeloid leukemia	2002	About 15	Short	Isfahan province	665 veterans	+
[23]	Davoudi	BCC	2006	10-15	Short	17 provinces	9605 veterans	–
[24]	Mortazavi	BCC and squamous cell carcinoma	2005	14-30	Short	Different provinces	800 veterans	+

SM=Sulfur mustard, BCC=Basal cell carcinoma

Lung cancers

Hosseini-khalili *et al*. conducted a molecular study on 20 Iranian male patients with lung cancer who had a history of single high-dose exposure to SM during Iraq-Iran war.[7] Considering DNA sequence analysis, some of the patients showed mutations related to SM.

Their study showed that single high-dose exposure to this agent could relate to lung cancer.[7]

Hematologic malignancies

Zakeri Nia *et al*. studied 3000 veterans from the Fars Province in Iran more than 15 years post their exposure to mustard gas. They evaluated relative risks (RRs) of aplastic anemia and hematologic malignancies and reported that exposure to mustard gas caused aplastic anemia (RR = 19) and blood malignancies including acute nonlymphocytic leukemia (RR = 8), acute lymphocytic leukemia (RR = 11), chronic myeloid leukemia (CML) (RR = 8), hairy cell leukemia (RR = 11), Hodgkin's lymphoma (RR = 5), non-Hodgkin's lymphoma (RR = 2), and intestinal Mediterranean lymphoma (RR = 13).[21]

Ghanei and Vosoghi evaluated the leukocyte alkaline phosphatase (LAP) activity of 665 chemically injured veterans and performed further cytochemical studies on the positive cases. Among the victims, nine cases had a decreased LAP, and two of them suffered from a CML. They reported a higher incidence of CML among the veterans exposed to mustard gas rather than normal population.[22]

Skin cancers

Davoudi *et al*. evaluated 9,605 chemically injured veterans 10–15 years after their exposure to SM from 17 provinces of Iran in 2006. Although they found four cases of basal cell carcinoma (BCC) among the victims, there was no statistically significant difference between the patients and the general population.[23] In another study, Mortazavi *et al*. assessed 800 chemically injured veterans 14–30 years after exposure in 2005. They found only one case of BCC and one case of squamous cell carcinoma among the veterans.[24]

DISCUSSION

SM can increase the cytotoxic T-cells and reduce natural killer cells (NKCs).[25] NKCs are lymphocytes which can kill tumor cells. Animal studies have shown a critical role for NKCs in controlling tumor growth and metastasis providing new insights into the treatment of human cancers.[26,27] Shaker *et al*. showed that the immune system of the chemically injured people was still impaired 10 years after exposure to SM.[26]

Regarding the reviewed studies and existing evidence, the relationship between chronic exposure to SM and incidence of various cancers cannot be ignored.[28] Ghanei and Harandi have confirmed this idea for lung cancers and mentioned that SM is an alkylating agent with potentially carcinogenic property in the respiratory tract.[29] Once SM microparticles reach to small bronchioles, their effects start happening.[30] Gene mutation is one of the late effects of SM causing pulmonary cancer.[30] Balali-Mood and Hefazi also mentioned bronchogenic carcinoma as a late complication of SM.[11] Likewise, they reported BCC, Bowen's carcinoma, and spinocellular skin cancer due to chronic exposure to mustard gas.[11]

We believe that when we are going to justify the relationship between acute exposure to SM and various cancers, one should be more cautious. Indeed, only a few original studies found such a relationship. For instance, although Zafarghandi *et al*. found the increased age-specific incidence rates of cancer, their results showed no evidence of increased age-adjusted incidence rate for specific cancer types.[10] Similarly, Hosseini-khalili *et al*. conducted a molecular study on only 20 veterans.[7] Moreover, Ghanei and Vosoghi found only 2 CML cases among 665 patients. They also mentioned that their

results should be cautiously interpreted due to some confounding factors within their study.[22] Accordingly, Davoudi *et al*. did not find any statistically significant difference between 9605 chemically injured veterans and general population according to BCC prevalence.[23] Furthermore, Mortazavi *et al*. found only one case of SCC and one case of BCC among 800 veterans.[24]

One follow-up study conducted in 1955 on soldiers who were exposed to SM during the World War I showed that mustard gas had no effect on the development of lung cancer.[16] Hadi *et al*. conducted a case–control study of 321 children younger than 15 years. They were 107 AML and all cases and 214 controls. They compared some variables between the two groups such as the history of attending in chemical war by the patients' fathers. Seven patients in the case group and three patients in the control group had such a history. They showed a significant odds ratio (4.9) of acute leukemia among the cases compared to the controls.[31]

Furthermore, Nik Siyar *et al*. compared 237 chemically injured and 202 healthy individuals showed that two hematologic indicators, hypogranulated neutrophils (the G-score) and percentage of polaroid cells, were significantly more among exposed people to SM than healthy individuals.[32] They suggested that the exposed people should be followed up for myelodysplastic syndromes in future.

Likewise, Maleki *et al*. reported a case of merkel cell carcinoma (MCC) in the place of mustard scar, 21 years after the exposure. MCC is an invasive primary neuroendocrine and nonmelanoma skin carcinoma.[33]

Considering our results although mustard gas is a proven carcinogenic agent in chronic situations, there are conflicting views in relation to the carcinogenicity of acute exposure to this substance.[16,20]

This review pulls together a broad array of data in an attempt to address whether acute SM exposure enhances long-term cancer risk among the survivors or not. However, confirming this idea is very difficult because cancer takes years/decades to develop, complicating the ability to directly link cancer onset with SM exposure. In addition, to prove any causal inference, we need vigorous evidence based on principles such as Bradford Hill's criteria.[34] At present, there is no sufficient evidence to substantiate such a relationship to underlying an increased cancer risk among SM survivors with a history of acute exposure to SM.

CONCLUSIONS

The relationship between chronic exposures to mustard gas and some types of cancers are well- documented so far. The respiratory system is more susceptible organ to cancer rather than others. The cancers occur through long-term and continuous exposure rather than an acute single-dose exposure.

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Conflicts of interest
There are no conflicts of interest.

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