Veterans with Agent Orange Exposure Have a Shorter Latency from Exposure to Diagnosis of Indolent B-cell Lymphoid Malignancies Compared to Unexposed Veterans

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Background

During the Vietnam War, Operation Ranch Hand (1962-1971) involved spraying Agent Orange (AO) in heavily forested areas. AO exposure has been associated with a higher risk of developing lymphoid malignancies, such as lymphomas and chronic lymphocytic leukemia [1].

Previous studies have grouped lymphoid malignancies in aggregate, making it difficult to understand the biologic differences. Military exposures are hard to define and measure, making it difficult to calculate the latency from exposure to diagnosis.

Our objective is to identify differences in outcomes in Veterans with assumed AO exposure who develop indolent B-cell lymphoid malignancies (IBCL) compared to unexposed veterans during the same period of military enlistment.

Materials & Methods

This is a retrospective case-case study of veterans who served between January 9, 1962, and May 7, 1975, and have a diagnosis of an IBCL.

Data were abstracted from the national Veteran Health Administration (VHA) records.

Descriptive statistics were used to describe patient characteristics, including gender, race, ethnicity, branch of service, tobacco use, stage, performance status, median age at diagnosis, latency from enlistment/exposure to diagnosis, and causes of death.

Latency from enlistment to diagnosis was calculated for unexposed patients. In those with documented AO exposure, latency was calculated from combat to diagnosis.

[1] National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Veterans and Agent Orange: Update 11 (2018).

Results

Table 1. Patient characteristics

Characteristics	Vietnam veterans (n=17175)	AO unexposed (n=11942)	AO exposed (n=5233)
Male gender, n (%)	16928 (99%)	11699 (98%)	5229 (99.9%)
Race			
White	13574 (87%)	9318 (87%)	4256 (88%)
Black	1703 (11%)	1228 (11%)	475 (10%)
Native Hawaiian/PI	97 (0.6%)	76 (0.7%)	21 (0.4%)
American Indian	95 (0.6%)	64 (0.6%)	31 (0.6%)
More than 1 (>1)	77 (0.5%)	55 (0.5%)	22 (0.4%)
Asian	29 (0.2%)	18 (0.2%)	11 (0.2%)
Missing	[1600]	[1183]	[417]
Ethnicity			
Not Hispanic	15,307 (97%)	10585 (97%)	4722 (97%)
Hispanic	554 (3%)	397 (4%)	157 (3%)
Missing	[1314]	[960]	[354]
Branch of Service			
Army	8261 (54%)	5527 (51%)	2734 (59%)
Navy	2888 (19%)	2175 (20%)	713 (15%)
Air Force	2340 (15%)	1940 (18%)	400 (9%)
Marine Corps	1710 (11%)	1005 (9%)	705 (15%)
Other or >1	211 (1%)	159 (1%)	52 (1%)
Missing	[1765]	[1136]	[629]
Tobacco use			
Previous user	6091 (41%)	4157 (40%)	1934 (43%)
Current user	4971 (34%)	3540 (34%)	1431 (32%)
Never user	3771 (25%)	2636 (26%)	1135 (25%)
Missing	[2342]	[1609]	[733]
Stage			
4	2703 (32%)	1900 (32%)	803 (31%)
1	1899 (22%)	1321 (22%)	578 (22%)
0	1538 (18%)	1031 (17%)	507 (19%)
3	1504 (18%)	1070 (18%)	434 (17%)
2	916 (11%)	625 (11%)	291 (11%)
Missing	[8615]	[5995]	[2620]
Performance status			
0	2549 (53%)	1665 (52%)	884 (57%)
1	1711 (36%)	1192 (37%)	519 (33%)
2	368 (8%)	260 (8%)	108 (7%)
3	116 (2%)	79 (2%)	37 (2%)
4	21 (0.4%)	15 (0.5%)	6 (0.4%)
Missing	[12410]	[8731]	[3679]
Causes of death			
Alive, censored	8568 (57%)	5708 (54%)	2860 (62%)
Neoplasm	4295 (28%)	3104 (30%)	1191 (26%)
Other	2237 (15%)	1687 (16%)	550 (12%)
Missing	[2075]	[1443]	[632]

There was no statistically significant difference between the median age at diagnosis in patients with and without AO exposure (66 years vs 65 years, p=.3464).

The median latency from combat exposure in AO lymphoid malignancies to diagnosis was 42 years (range, 10-59) vs 44 years (2-59) from enlistment to diagnosis in unexposed lymphoid malignancies (p<.0001).

The most common subtypes of IBCL and respective latencies (AO vs unexposed) were:

- Chronic lymphocytic leukemia (52%)
  - 43 years (range 10–57) vs. 45 (10–60), p<.0001
- Follicular lymphoma (22%)
  - 41 years (12–59) vs. 44 (2–59), p<.0001
- Marginal zone lymphoma (9%)
  - 44 years (26–55) vs. 45 (15–59), p=.017
- Mantle cell lymphoma (8%)
  - 43 years (range 25–54) vs. 45 (21–59), p=.0004
- Lymphoplasmacytic lymphoma (5%)
  - 47 years (24–53) vs. 46 (18–59), p=.4583

In patients with treatment data available (n=15,701), most patients did not receive treatment (63%). A minority of patients refused treatment (0.6%) or died before getting treatment (0.1%). Treatment was recommended in some patients (0.5%), but it was not given or unknown if administered.

Using a Cox proportional hazard model, parameters associated with higher risks of death included age at diagnosis (HR, 1.067; 95%CI, 1.04–1.09), tobacco use (HR, 2.112; 95%CI, 1.739–2.565), more advanced stage (HR, 1.158; 95%CI, 1.098–1.220), and worse performance status (HR, 1.512; 95%CI, 1.382–1.655).

AO exposure was not associated with a significantly higher risk of death (HR, 1.069; 95%CI, 0.885–1.291).

Summary

Half of the patients were diagnosed with advanced (stage 3-4) disease, but a majority (~80%) had an excellent performance status (ECOG 0-1).

AO exposure is associated with a shorter latency from combat to diagnosis compared to that seen in patients without AO (enlistment to diagnosis).

When considering age at diagnosis, tobacco use, stage, performance status, AO exposure did not result in a worse overall survival.

Discussion and Future Directions

The shorter latency in AO-exposed veterans suggests that there may be differences in the etiopathogenesis of IBCL between the two groups. Future studies should investigate this possibility, which may also better inform the selection of biological/targeted therapies.

More work needs to be done to document, characterize, and quantify exposures, ideally starting at the time of exposure for more meaningful analyses.

It is important to understand the reasons why certain individuals/groups are sent to theaters of conflict, because this is an important confounder in determining the contribution of military exposures to the development and outcomes of diseases.

Acknowledgements

This work was supported by the VA Long Beach Healthcare System, VA Informatics and Computing Infrastructure (VINCI), National Death Index, Lymphoma Research Foundation, and University of California, Irvine Department of Medicine.