**Supplementary Content**

YJ Kim, HJ Yang, CH Won, SE Chang, MW Lee, WJ Lee. Clinicoprognostic study of hydroa vacciniforme-like lymphoproliferative diseases: A systematic review.

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**eReferences.**

This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1. Search Strategy for MEDLINE**

|  |  |
| --- | --- |
| #1 | "Hydroa Vacciniforme"[Mesh] |
| #2 | "Hydroa Vacciniforme"[TW] OR "hydroa vacciniform"[TW] |
| #3 | #1 OR #2 |
| #4 | "Lymphoproliferative Disorders"[Mesh] |
| #5 | Lymphoproliferativ\*[TW] OR Lymphoma\*[TW] OR eruption\*[TW] |
| #6 | #4 OR #5 |
| #7 | #3 AND #6 |
| #8 | #7 AND English[Lang] |

**eTable2. Methodologic Quality Assessment for Each Included Study**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Did the patient(s) represent all or consecutive case(s) of the medical center? | Was the diagnosis correctly made? | Were other important diagnoses excluded? | Were all important data cited in the report? | Was the outcome correctly ascertained? | Overall methodologic quality |
| Barrionuevo 2002 | Y | Y | Y | Y | Y | Good |
| Beltran 2014 | Y | Y | Y | Y | Y | Good |
| Boddu 2015 | N | Y | Y | Y | Y | Moderate |
| Brauns 2012 | N | Y | Y | Y | Y | Moderate |
| Chee 2016 | N | Y | Y | Y | Y | Moderate |
| Chen 2002 | N | Y | Y | Y | Y | Moderate |
| Chen 2016 | Y | Y | Y | Y | Y | Good |
| Chen 2018 | N | Y | Y | Y | Y | Moderate |
| Cho 2000 | Y | Y | Y | Y | Y | Good |
| Cho 2001 | N | Y | Y | Y | Y | Moderate |
| Cho 2004 | N | Y | Y | Y | Y | Moderate |
| Cohen 2016 | N | Y | Y | Y | Y | Moderate |
| Cohen 2019 | Y | Y | Y | Y | Y | Good |
| Doeden 2008 | Y | Y | Y | Y | Y | Good |
| El-Mallawany 2011 | N | Y | Y | Y | Y | Moderate |
| Feng 2008 | Y | Y | Y | Y | Y | Good |
| Folkes 2018 | N | Y | Y | Y | Y | Moderate |
| Franzblau 2018 | N | Y | Y | Y | Y | Moderate |
| Guo 2019 | Y | Y | Y | Y | Y | Good |
| Haddad 2014 | N | Y | Y | Y | Y | Moderate |
| Hann 1991 | Y | Y | Y | Y | Y | Good |
| Heo 2003 | N | Y | Y | Y | Y | Moderate |
| Hijazi 2015 | N | Y | Y | Y | Y | Moderate |
| Hirai 2012 | Y | Y | Y | Y | Y | Good |
| Huang 2014 | Y | Y | Y | Y | Y | Good |
| Huh 2009 | N | Y | Y | Y | Y | Moderate |
| Iwatsuki 1999 | Y | Y | Y | Y | Y | Good |
| Iwatsuki 2006 | Y | Y | Y | Y | Y | Good |
| Jung 2015 | N | Y | Y | Y | Y | Moderate |
| Katagiri 2003 | N | Y | Y | Y | Y | Moderate |
| Kawabe 2012 | Y | Y | Y | Y | Y | Good |
| Kim 1998 | N | Y | Y | Y | Y | Moderate |
| Kim 2015 | N | Y | Y | Y | Y | Moderate |
| Kim 2017 | N | Y | Y | Y | Y | Moderate |
| Lee 2012 | N | Y | Y | Y | Y | Moderate |
| Lee 2016 | N | Y | Y | Y | Y | Moderate |
| Levoska 2018 | N | Y | Y | Y | Y | Moderate |
| Li 2013 | Y | Y | Y | Y | Y | Good |
| Li 2018 | N | Y | Y | Y | Y | Moderate |
| Lim 2017 | N | Y | Y | Y | Y | Moderate |
| Lin 2010 | N | Y | Y | Y | Y | Moderate |
| Liu 2020 | N | Y | Y | Y | Y | Moderate |
| Long 2018 | N | Y | Y | Y | Y | Moderate |
| Lyapichev 2020 | Y | Y | Y | Y | Y | Good |
| Lysell 2009 | N | Y | Y | Y | Y | Moderate |
| Magana 1998 | N | Y | Y | Y | Y | Moderate |
| Magana 2016 | Y | Y | Y | Y | Y | Good |
| Merino 2018 | N | Y | Y | Y | Y | Moderate |
| Miranda 2018 | N | Y | Y | Y | Y | Moderate |
| Montalvo 2016 | Y | Y | Y | Y | Y | Good |
| Mose 2014 | N | Y | Y | Y | Y | Moderate |
| Nitta 2005 | Y | Y | Y | Y | Y | Good |
| Nomura 2014 | N | Y | Y | Y | Y | Moderate |
| Nomura 2015 | N | Y | Y | Y | Y | Moderate |
| Oono 1986 | N | Y | Y | Y | Y | Moderate |
| Park 2010 | Y | Y | Y | Y | Y | Good |
| Park 2013 | N | Y | N | Y | Y | Poor |
| Plaza 2015 | Y | Y | Y | Y | Y | Good |
| Qiao 2016 | N | Y | Y | Y | Y | Moderate |
| Quintanilla-Martinez 2013 | Y | Y | Y | Y | Y | Good |
| Rhodes 1998 | Y | Y | N | Y | Y | Moderate |
| Rodriguez-Pinilla 2010 | Y | Y | Y | Y | Y | Good |
| Rodriguez-Pinilla 2011 | Y | Y | Y | Y | Y | Good |
| Roy 2019 | N | Y | Y | N | Y | Poor |
| Ruan 2020 | Y | Y | Y | N | Y | Moderate |
| Ruiz-Maldonado 1995 | Y | Y | N | N | Y | Poor |
| Sangueza 2013 | Y | Y | Y | Y | Y | Good |
| Sangwan 2017 | N | Y | Y | Y | Y | Moderate |
| Santos 2013 | N | Y | Y | Y | Y | Moderate |
| Satoh 2002 | N | Y | Y | Y | Y | Moderate |
| Shi 2014 | N | Y | Y | Y | Y | Moderate |
| Shin 2016 | N | Y | Y | Y | Y | Moderate |
| Steger 1988 | N | Y | Y | Y | Y | Moderate |
| Stratigos 2003 | Y | Y | Y | N | Y | Moderate |
| Takeuchi 2011 | N | Y | Y | Y | Y | Moderate |
| Tanaka 2012 | N | Y | Y | Y | Y | Moderate |
| Toksoy 2017 | N | Y | Y | Y | Y | Moderate |
| Verneuil 2010 | Y | Y | Y | Y | Y | Good |
| Wada 2012 | N | Y | Y | Y | Y | Moderate |
| Wada 2018 | N | Y | Y | Y | Y | Moderate |
| Wang 2013 | N | Y | Y | Y | Y | Moderate |
| Wang 2013 | N | Y | Y | Y | Y | Moderate |
| Wang 2014 | Y | Y | Y | Y | Y | Good |
| Wang 2018 | Y | Y | Y | Y | Y | Good |
| Wang 2019 | Y | Y | Y | Y | Y | Good |
| Wen 2018 | N | Y | Y | Y | Y | Moderate |
| Wen 2019 | Y | Y | Y | Y | Y | Good |
| Wong 2001 | Y | Y | Y | Y | Y | Good |
| Wu 2007 | N | Y | Y | Y | Y | Moderate |
| Xu 2010 | Y | Y | Y | Y | Y | Good |
| Xue 2019 | Y | Y | Y | Y | Y | Good |
| Yang 2014 | Y | Y | Y | Y | Y | Good |
| Yoon 2001 | N | Y | Y | Y | Y | Moderate |
| Yoon 2005 | N | Y | Y | Y | Y | Moderate |
| Zamecki 2010 | N | Y | Y | Y | Y | Moderate |
| Zeng 2012 | N | Y | Y | Y | Y | Moderate |
| Zhang 2013 | N | Y | Y | Y | Y | Moderate |
| Zhang 2018 | Y | Y | Y | Y | Y | Good |

**Supplementary Table 1. Characteristics of the patients of the Asan Medical Center**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patient** | **Sex/ Age** | **Onset**  **(years ago)** | **Disease classification and Clinical features** | **Immunohistochemistry/EBV** | **Prognosis** | **Treatment** |
| 1 | F/9 | 3 | Classic HV/papules with crust on the whole body, pruritus, photosensitivity | - | Recurrent eruption after 6 years | Anti-histamine |
| 2 | F/71 | 5 | HVLL/papules with crust on the head and neck, pruritus and pain, facial edema, lymphadenopathy | CD3+, CD4-, CD8-, CD56-, CD20-, CD2+, CD5-, TIA+, Ki-67: 90%, TCR rearrangement +, EBV: 271.2 copies/mL | Progression after 1 year, death after 3 years | Prednisolone, hydroxychloroquine, anti-histamine, topical pimecrolimus |
| 3 | F/40 | 20 | HVLL/papules with crust on the head and neck, photosensitivity | CD3+, CD4+, CD8+, CD20-, Ki-67: 30%, TCR rearrangement +, EBV: 871.8 copies/mL | Progression after 5 years | Minocycline, ibuprofen |
| 4 | F/32 | 0.25 | Severe HV/papules with crust and erosion on the head and neck, pruritus and pain, facial edema, fever, mosquito hypersensitivity | CD3+, CD4-, CD8-, CD56+, CD20-, TIA+, Ki-67: 20%, EBV: 1,069 copies/mL | Death after 3 years | Tetracycline, ibuprofen |
| 5 | F/66 | 20 | HVLL/papules with crust and ulcer on the head, neck, and upper extremities, pruritus and pain, facial edema, fever, weight loss, night sweats, photosensitivity | CD3+, CD4+, CD8+, TCR rearrangement +, EBV: 206,939 copies/mL | Death after 3 years | Hydroxychloroquine, anti-histamine |

HV, Hydroa vacciniforme; HVLL, HV-like T cell lymphoma; EBV, Epstein‒Barr virus; TIA, T-cell intracytoplasmic antigen; TCR, T-cell receptor

**Supplementary Table 2. Treatment data available for 264 HVLPD patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment** | **Classic HV (%)** | **Severe HV/HVLL (%)** | **Total (%)** |
| Data available, *n* | 23 (100) | 241 (100) | 264 (100) |
| Sun protection, Anti-histamine, NSAID | 12 (52.2) | 12 (5.0) | 24 (9.1) |
| Topical steroid | 6 (26.1) | 6 (2.5) | 12 (4.5) |
| Chemotherapy | 0 | 92 (38.2) | 92 (34.8) |
| Systemic steroid | 2 (8.7) | 105 (43.6) | 107 (40.5) |
| Anti-malarial agents | 3 (13.0) | 14 (5.8) | 17 (6.4) |
| Interferon | 0 | 35 (14.5) | 35 (13.3) |
| Thalidomide | 0 | 28 (11.6) | 28 (10.6) |
| Cyclophosphamide | 0 | 43 (17.8) | 43 (16.3) |
| Antibiotics | 0 | 18 (7.5) | 18 (6.8) |
| Anti-herpetic agents | 2 (8.7) | 21 (8.7) | 23 (8.7) |
| Bone marrow transplant | 0 | 15 (6.2) | 15 (5.7) |
| Intravenous immunoglobulin | 0 | 11 (4.6) | 11 (4.2) |
| Acitretin/Retinoic acid | 0 | 14 (5.8) | 14 (5.3) |
| Chinese herbal medicine | 0 | 11 (4.6) | 11 (4.2) |
| Complete response + Partial response | 8 (88.9) | 95 (60.9) | 103 (62.4) |
| Stable disease + Progressive disease | 1 (11.1) | 61 (39.1) | 62 (37.6) |

HV, Hydroa vacciniforme; HVLL, HV-like T cell lymphoma; NSAID, non-steroidal anti-inflammatory drugs

**Supplementary Table 3.** **Treatment and response data available for classic HV patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment** | **Classic HV (%)** | **CR + PR** | **SD + PD** |
| Data available, *n* | 9 (100) | 8 (88.9) | 1 (11.1) |
| Sun protection, Anti-histamine, NSAID | 6 (100) | 5 (83.3) | 1 (16.7) |
| Topical steroid | 2 (100) | 2 (100) | 0 |
| Chemotherapy | 0 | 0 | 0 |
| Systemic steroid | 0 | 0 | 0 |
| Anti-malarial agents | 1 (100) | 1 (100) | 0 |
| Interferon | 0 | 0 | 0 |
| Thalidomide | 0 | 0 | 0 |
| Cyclophosphamide | 0 | 0 | 0 |
| Antibiotics | 0 | 0 | 0 |
| Anti-herpetic agents | 0 | 0 | 0 |
| Bone marrow transplant | 0 | 0 | 0 |
| Intravenous immunoglobulin | 0 | 0 | 0 |
| Acitretin/Retinoic acid | 0 | 0 | 0 |
| Chinese herbal medicine | 0 | 0 | 0 |

HV, Hydroa vacciniforme; NSAID, non-steroidal anti-inflammatory drugs; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

**Supplementary Table 4.** **Treatment and response data available for severe HV/HVLL patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment** | **Severe HV/**  **HVLL (%)** | **CR + PR** | **SD + PD** |
| Data available, *n* | 47 (100) | 36 (76.6) | 11 (23.4) |
| Sun protection, Anti-histamine, NSAID | 0 | 0 | 0 |
| Topical steroid | 1 (100) | 1 (100) | 0 |
| Chemotherapy | 19 (100) | 10 (52.6) | 9 (47.4) |
| Systemic steroid | 6 (100) | 5 (83.3) | 1 (16.7) |
| Anti-malarial agents | 2 (100) | 2 (100) | 0 |
| Interferon | 4 (100) | 4 (100) | 0 |
| Thalidomide | 2 (100) | 2 (100) | 0 |
| Cyclophosphamide | 0 | 0 | 0 |
| Antibiotics | 0 | 0 | 0 |
| Anti-herpetic agents | 5 (100) | 5 (100) | 0 |
| Hematopoietic stem cell transplantation | 4 (100) | 4 (100) | 0 |
| Intravenous immunoglobulin | 2 (100) | 2 (100) | 0 |
| Acitretin/Retinoic acid | 0 | 0 | 0 |
| Chinese herbal medicine | 2 (100) | 1 (50) | 1 (50) |

HV, Hydroa vacciniforme; HVLL, HV-like T cell lymphoma; NSAID, non-steroidal anti-inflammatory drugs CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

**Supplementary Table 5. Risk factors for the progression and development of secondary lymphoma and parameters affecting overall survival**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Risk factors for progression** | | | | | | | |
|  | | | Univariable analysis | | | | |
|  | | | HR (95% CI) | | | | *P* value |
| Severe HV/HVLL | | | 1.59 (1.23‒2.05) | | | | < 0.001\*\* |
| Facial edema  Onset age > 9 years  CD8-positivity in tumor tissues  Dual CD4/CD8-negativity in tumor tissues  Non-Whites† | | | 6.36 (1.75–23.10)  4.35 (1.56‒12.08)  0.14 (0.03‒0.76)  0.67 (0.50‒0.89)  10.64 (2.76‒41.02) | | | | 0.003\*\*  0.003\*\*  0.014\*  0.023\*  < 0.001\*\* |
|  | | Multivariable analysis | | | | | |
|  | | HR (95% CI) | | *P* value | | | |
| Facial edema | | | 6.36 (1.75‒23.10) | 0.005\*\* | | | |
| **Risk factors for secondary lymphoma** | | | | | | | |
|  | | | Univariable analysis | | | | |
|  | | | HR (95% CI) | | | | *P* value |
| Severe HV/HVLL | | | 7.89 (1.06–58.61) | | | | 0.017\* |
| **Risk factors affecting overall survival** | | | | | | | |
|  | | | Univariable analysis | | | | |
|  | | | HR (95% CI) | | | | *P* value |
| Severe HV/HVLL  Facial edema  Hypersensitivity to mosquito bite  CD8-positivity in tumor tissues  Dual CD4/CD8-negativity in tumor tissues  Non-White | | | 1.14 (1.09‒1.21)  5.73 (3.01‒10.93)  0.40 (0.17‒0.95)  0.40 (0.22‒0.76)  6.21 (2.66‒14.48)  14.13 (1.87‒106.26) | | | | < 0.001\*\*  < 0.001\*\*  0.036\*  0.004\*\*  < 0.001\*\*  0.001\*\* |
|  | | | Multivariable analysis | | | | |
|  | | | HR (95% CI) | *P* value | | | |
| Facial edema | | | 5.31 (2.00‒14.12) | | | | 0.001\*\* |
| Dual CD4/CD8-negativity in tumor tissues | | | 7.43 (2.21‒24.97) | | | | 0.001\*\* |

\*Statistically significant, †Asian and Latin American

HV, Hydroa vacciniforme; HVLL, HV-like T cell lymphoma; CI, confidence interval; HR, hazard ratio

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