Clinical characteristics and long-term outcomes of warm-type autoimmune hemolytic anemia

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Objectives: To study the clinical manifestations, outcomes, and survival of warm-type autoimmune hemolytic anemia (AIHA) patients.

Methods: This study was a retrospective single-center study from 2002 to 2013. Clinical data of AIHA patients were reviewed and analyzed.

Results: One hundred and one patients were included, of whom 77% were female with a median age of 43 years. Primary AIHA was found in 61% of the patients. The secondary causes were systemic lupus erythematosus (SLE) (64%), solid malignancies (13%), lymphomas (10%), drugs (8%), and infections (5%). Most patients (96%) responded to steroids, which were not different between primary and secondary AIHA. Second-line treatments were required in 33 patients (33%). The indications were steroid dependence (58%), relapse (30%), and others (12%). The most common second-line treatment was cyclophosphamide (52%). The response rate for second-line treatments was 93%. Relapse occurred in 50 patients (50%) in which 58% occurred more than 3 years after diagnosis. The SLE patients relapsed and received second-line therapy more than the non-SLE group (P < 0.001). At the median 53-month follow-up, the overall survival (OS) was 84%. The independent risk factors for OS were age more than 50 years and malignancy. Sepsis was the most common cause of death.

Discussion and conclusion: AIHA has a good prognosis and long-term survival especially in young patients without malignancy. Most patients have responded initially to steroids and have a high response rate to second-line therapy. Carefully adjusted and rapid taper of immunosuppressant is necessary to avoid sepsis complications.

Keywords: Autoimmune hemolytic anemia (AIHA), Warm-type autoimmune hemolytic anemia, Primary autoimmune hemolytic anemia, Secondary autoimmune hemolytic anemia

Introduction

Warm-type autoimmune hemolytic anemia (AIHA) is an uncommon disease in which antibodies react with self-antigen on red blood cells at body temperature.¹,² The incidence in the USA is 0.8 per 100 000 person-year.³ Although AIHA is not a common disease, there are many challenges regarding laboratory diagnosis and management such as therapeutic options and blood transfusions.⁴,⁵ Moreover, AIHA is associated with other secondary causes, for instance, collagen vascular diseases, lymphoproliferative diseases, and solid malignancies in more than half of the patients that required investigation by the physicians.⁶ Corticosteroid is the first-line treatment of warm-type AIHA.⁴,⁷–⁹ However, about one-third of the patients have steroid dependence or steroid resistance which require second-line treatment.⁵ The management options for both situations include immunosuppressive drugs, for example, cyclophosphamide, azathioprine, cyclosporine, and mycophenolate mofetil, splenectomy, rituximab (anti-CD20 monoclonal antibody), danazol, intravenous immunoglobulin, and hematopoietic stem cell transplantation.⁴,⁷–⁹
Owing to the rarity of this disease, limited numbers of studies regarding clinical manifestations, etiologies, second-line treatment, and long-term outcomes were available.\textsuperscript{10,12} One study from Thailand in 1977 showed that Thai AIHA patients were younger with female predominance and had less incidence of cold-type AIHA compared with Caucasians.\textsuperscript{10}

In this study, the authors present the clinical presentation, secondary causes, and long-term treatment outcomes of warm-type AIHA at Chiang Mai University Hospital, Thailand.

**Research objectives**

This study examined clinical manifestations, secondary causes, both first-line and second-line therapies, response rate, relapsed rate, and survival of warm-type AIHA patients.

**Material and methods**

**Research methodology**

This was a retrospective study conducted at Chiang Mai University Hospital, Chiang-Mai, Thailand. Patients who were diagnosed with warm-type AIHA from 1 January 2002 through 31 December 2013 were enrolled. All patients need to meet all inclusion criteria to be enrolled into the study. Inclusion criteria were age more than 15 years with a diagnosis of warm-type AIHA confirmed by hematologist. The diagnosis was based on evidences of hemolytic anemia such as increased polychromasia with or without nucleated red blood cells as well as the presence of microspherocytes on blood smear, reticulocytosis, indirect hyperbilirubinemia, and elevation of serum lactate dehydrogenase in addition to a positive polyclonal (IgG and C3d) of direct antiglobulin (Coombs') test.\textsuperscript{8} There were no exclusion criteria for this study.

**Data collection and definition**

The data were collected from medical records of patients with warm-type AIHA including age, sex, date of diagnosis and last follow-up, baseline hemoglobin (Hb), secondary causes, first-line and second-line treatments, response to treatment, relapse, time to relapse, and mortality.

The definition of steroid responsiveness was provided by Hb more than 10 g/dl after therapy with prednisolone 1 mg/kg/day within 3 weeks. Relapse was defined by Hb decreased to less than 10 g/dl during maintenance treatment of prednisolone less than 15 mg/day and due to AIHA not from other causes such as blood loss. Steroid dependence was the inability to taper prednisolone to a dose lower than 15 mg/day in order to maintain Hb levels of at least 10 g/dl.\textsuperscript{2,8}

Overall survival (OS) was defined as time since diagnosis to relapse or death. All cases that were lost to follow-up or were referred to other hospitals were searched in the civil registration of Thailand to identify survival status and cause of death.

**Statistical analysis**

Demographic data and laboratory data were presented as descriptive statistics including frequency, percentage, mean, median, and range. Comparison between two groups was performed by the Chi-square or Fisher's exact test depending on the type of variables with statistical significance at P-value less than 0.05. The survival analysis was determined by the Kaplan-Meier curve and log-rank test with P-value less than 0.05 to determine statistical significance. The factors that affected the outcomes were analyzed with multivariate analysis using Cox regression model. All of the statistical analyses were performed by SPSS (SPSS for Windows version 20 IBM Inc.).

**Results**

**Demographic data and clinical characteristics**

One hundred and one warm-type AIHA patients were enrolled into this study. Seventy-eight patients (77.2%) were female with a mean and median age of 43.93 and 43 years, respectively (range 15–83 years), as shown in Table 1. The diagnosis was made before January 2003 in 36 patients (35.6%) and during this study period in 65 patients (64.4%).

The mean and median Hb were 5.32 and 5.4 g/dl, respectively (range 2–10 g/dl). Sixty-two patients (61.4\%) were identified with primary AIHA, whereas 39 patients (38.6\%) had secondary AIHA. The most common cause of secondary AIHA was SLE in 25 patients (64.1\%) that almost all except one occurred in female patients. SLE was also the most common cause of secondary AIHA in females (77.4\%), whereas lymphoproliferative diseases (NHL including chronic lymphocytic leukemia (CLL)) were most common in males (four patients).

Secondary causes of AIHA occurred commonly in a younger age group. The proportion of secondary AIHA in the age groups of 15–50 years and 51–70 years were 19/31 (61\%) and 10/26 (38.5\%), respectively (P = 0.006). SLE also occurred predominantly in a younger age group (less than 50 years) in 21 patients (84\%). On the other hand, malignancies both solid and hematologic malignancies were found as secondary AIHA in seven older patients (50\%) compared with two younger patients (8\%).

**Steroid responsiveness**

Clinical outcomes of warm-type AIHA are shown in Table 2. Ninety-nine patients received corticosteroids for treatment of warm-type AIHA, while two other
patients with drug-induced AIHA received only blood transfusions and discontinuation of the offending drugs. Ninety-five patients (96%) were steroid responsive, whereas four patients (two primary and two secondary AIHA) were not responsive. The rates of steroid responsiveness in primary and secondary AIHA were not statistically different ($P = 0.172$).

**Second-line treatment**

Thirty-three patients (33.3%) received second-line treatments after corticosteroids. The indication for the initiation of second-line treatments was steroid dependence in 19 patients (19.1%), relapse in ten patients (10.1%), and other indications (such as for treatment of lupus nephritis) in four patients (4.0%). Cyclophosphamide and azathioprine were the most frequent medications utilized in 33 (53%) and 7 (21%) patients, respectively. Two patients received both immunosuppressive drugs. Response after second-line treatments occurred in 31 patients (93.9%). Two patients who did not respond received second-line treatments due to relapse in one patient and steroid dependence in one patient and occurred in both the primary (one patient) and secondary AIHA (one patient) groups.

Seventeen of the primary AIHA patients (27.4%) received second-line treatments, whereas 16 patients (41%) of secondary AIHA received second-line

| Table 1 Baseline characteristics of warm-type AIHA patients |
|-----------------|-----------------|
| **Baseline characteristics** | **N = 101** |
| **Sex** | |
| Female | 78 (77.2%) |
| Age (years) | |
| Median (range) | 43 (15–83) |
| Age group | |
| Less than 50 years | 64 (63.4%) |
| More than 50 years | 37 (36.6%) |
| Hemoglobin (g/dl) | 5.3 (2–10) |
| **Causes** | |
| Primary | 62 (61.4%) |
| Secondary | 39 (38.6%) |
| - SLE | 25/39 (64.1%) |
| - Solid cancer* | 5/39 (12.8%) |
| - NHL | 4/39 (10.3%) |
| - Drugs** | 3/39 (7.7%) |
| - Others*** | 2/39 (5.1%) |
| **Secondary causes according to sex: female** | |
| - SLE | 24/31 (77.4%) |
| - Solid cancer | 4/31 (12.9%) |
| - NHL | 0/31 (0.0%) |
| - Drugs | 2/31 (6.5%) |
| - Others | 1/31 (3.2%) |
| **Secondary causes according to sex: male** | |
| - SLE | 1/8 (12.5%) |
| - Solid cancer | 1/8 (12.5%) |
| - NHL | 4/8 (50%) |
| - Drugs | 1/8 (12.5%) |
| - Others | 1/8 (12.5%) |
| **Secondary AIHA from SLE according to age group:** | |
| Less than 50 years | 21/25 (84%) |
| More than 50 years | 4/25 (16%) |
| **Secondary AIHA from non-SLE according to age group:** | |
| Less than 50 years | 43/76 (56.6%) |
| More than 50 years | 33/76 (43.4%) |

*Solid cancer: CA breast (1), CA tongue (1), CA Ovary (1), CA colon (2).
**Drugs: Ceftazidime (1), Isoniazid (1), Telmisartan (1).
***Others: Viral pneumonia (1), NTM infection (1).
SLE: systemic lupus erythematosus; NHL: non-Hodgkin lymphoma; CA: cancer of; NTM: non-tuberculous mycobacterium.

| Table 2 Clinical outcomes of warm-type AIHA patients |
|-----------------|-----------------|
| **Clinical outcomes** | **N = 101** |
| **Steroid responsiveness** (two patients excluded who did not receive steroids) | |
| Overall | 95/99 (96.0%) |
| Primary AIHA | 60/62 (96.8%) |
| Secondary AIHA | 35/37 (94.6%) |
| **Second-line treatment** | 33 (32.7%) |
| **Indication** | |
| Steroid dependence | 19/33 (57.6%) |
| Relapse | 10/33 (30.3%) |
| Other indications | 4/33 (12.1%) |
| **Type** | |
| Cyclophosphamide | 17/33 (51.5%) |
| Azathioprine | 7/33 (21.2%) |
| Cyclosporine | 2/33 (6.1%) |
| Splenectomy | 2/33 (6.1%) |
| Danazol | 2/33 (6.1%) |
| Azathioprine + cyclophosphamide | 1/33 (3.0%) |
| Azathioprine + IVIG | 1/33 (3.0%) |
| MMF | 1/33 (3.0%) |
| **Second-line treatment according to underlying diseases** | |
| SLE | 16/25 (64.0%) |
| Non-SLE | 17/76 (22.4%) |
| Response to second-line treatment | 31/33 (93.9%) |
| **Relapse** | 50/101 (49.5%) |
| **Time to relapse** | |
| Within 1 year | 9/50 (18.0%) |
| 1–3 years | 12/50 (24.0%) |
| More than 3 years | 29/50 (58.0%) |
| **Association of relapse and causes of** | ($P = 0.4$) |
| AIHA | |
| Primary AIHA | 31/62 (50.0%) |
| Secondary AIHA | 19/39 (48.7%) |
| **Association of relapse and SLE** | ($P < 0.001$) |
| SLE | 18/25 (72.0%) |
| Non-SLE | 32/76 (42.1%) |
| **Association of relapse and second-line** | ($P < 0.001$) |
| drug use | |
| Yes | 28/33 (84.8%) |
| No | 22/68 (32.4%) |
| **Follow-up status** | |
| Regular follow-up | 64 (63.4%) |
| Loss to follow-up more than 1 year | 31 (30.7%) |
| **Refer** | 6 (5.9%) |
| **Survival status** | |
| Death | 20 (19.8%) |
| Alive | 68 (67.3%) |
| Unknown | 13 (12.9%) |
| **Death** | |
| Primary AIHA | 10/62 (16.1%) |
| Secondary AIHA | 10/39 (25.6%) |
| Malignancy | 5/9 (55.5%) |
| Non-malignancy | 5/30 (16.7%) |
| **Causes of death** | |
| Sepsis and septic shock | 6/20 (30.0%) |
| Acute coronary syndrome | 1/20 (5.0%) |
| Unknown | 15/20 (65%) |

IVIG, intravenous immunoglobulin.
treatments, which were not statistically different ($P = 0.156$). Sixty-four percent of the SLE group with AIHA received second-line treatments, which comprised 48% (16 out of 23 patients) of the patients who received second-line treatments. The analysis confirmed that SLE patients (64.0%) received more second-line therapies than non-SLE patients (22.4%) with secondary AIHA ($P < 0.05$).

**Relapse**
Relapse of AIHA occurred in 50 patients (49.5%). Most of the relapse events appeared after 3 years in 29 patients (58%) with the median time to relapse of 36 months as shown in Table 2. Thirty-one primary AIHA patients (50%) and 19 secondary AIHA patients (48.7%) experienced relapse, which showed no statistical difference ($P = 0.9$). Almost all except one secondary AIHA patients who relapsed had SLE, whereas the other patient had an underlying malignancy. Relapse significantly occurred more in SLE (18 out of 25 patients; 72%) compared with non-SLE patients (32 out of 76 patients; 42%) ($P = 0.01$). Age (more or less than 50 years) was not associated with the risk of relapse ($P = 0.896$).

Twenty-eight patients (56%) who relapsed received second-line treatment. The other patients were treated only by increasing the dose of corticosteroids. In non-relapse patients, only 5 out of 51 patients (9.8%) received second-line medication, which was significantly less than that in relapse cases ($P < 0.05$).

**Long-term follow-up and survival**
The median follow-up time of the patients in this study was 53 months. Thirty-seven patients lost to follow-up for more than 1 year included six patients who were transferred to other hospitals. The rate of loss to follow-up was not different between primary and secondary AIHA patients ($P = 0.145$).

For survival analysis, ten primary AIHA patients (16%) died, whereas five from nine (55%) secondary AIHA patients from malignancy and 5 out of 30 (17%) patients with secondary AIHA passed away from other causes. At the median follow up of 53 months, the 5 year overall survival (OS) of the entire population was 84%. The median OS was 295 months (95% CI 248–343). The most common cause of death was sepsis. Secondary AIHA from cancer had a higher mortality rate with a median OS of 25.5 months (95% CI 10.8–40.2; $P < 0.05$) compared with 311 months in non-cancer patients. There was no difference in the mortality rate between primary AIHA and secondary AIHA from non-malignancy causes as shown in Fig. 1.

There was no significantly different OS between relapse and non-relapse patients as well as between using second-line treatment and not ($P = 0.333$ and 0.228, respectively). Either indication of second-line treatment was steroid dependence or relapse, but the OS was not different ($P = 0.723$). Males had a slightly higher mortality rate than females ($P = 0.043$) and patients with an older age of more than 50 years had an increased mortality rate ($P = 0.001$) as shown in Fig. 2. The multivariate analysis revealed two independent risk factors of OS, which were age more than 50 years ($P = 0.033$; hazard ratio (HR) 3.09 (1.09–8.73)) and secondary AIHA from malignancies ($P = 0.03$; HR 4.06 (1.18–13.97)).
The EFS at the median follow-up time was 48% with a median EFS of 33 months and median relapse-free survival of 46 months (95% CI 25.64–66.36). From multivariate analysis, only age more than 50 years had an impact on EFS ($P = 0.009; \text{HR} = 2.08 (1.21–2.57))$. There was no significantly different EFS between primary and secondary AIHA ($P = 0.236$), sex ($P = 0.864$), and the presence of malignancy ($P = 0.121$).

**Discussion**

During the 12-year study period from 2002 to 2013, the majority of warm-type AIHA patients were female (77%) with median age of 43 years. Most of the patients (63.3%) were diagnosed when they were 50 years of age. Especially secondary AIHA from SLE which was more commonly found in young females, 68% of this group had an age that was less than 30 years. The baseline characteristics were comparable to the study by Baek et al that showed a median age of 48 years and female predominance. However, this Korean study had more female predominance (94%) compared with our study (77%). This could be explained by more SLE as a secondary cause of AIHA (56 and 25%).

Primary AIHA was found slightly more often than secondary AIHA with a ratio of 3:2. The most common cause of secondary AIHA was SLE (64%), which occurred predominately in females. As a result, physicians should look for the possibility of SLE in young women with AIHA. Moreover, AIHA is a common manifestation of SLE which accounted for 6% and continues to be one of the diagnostic criteria at Hb $12$ g/dl) of 50% and a partial response rate (Hb $10$ g/dl) of 32%. Our study used the response criteria at Hb $> 10$ g/dl. The slightly different response rate could be explained by different response criteria between studies. Moreover, the response and relapse criteria of our study used only cut-off value of hemoglobin rather than both cut-off value and hemoglobin-level change from baseline compared with other studies.

Second-line therapies were used in both primary and secondary AIHA. The indication to start second-line treatment was steroid dependence more than relapse. The rate of using second-line treatment in secondary AIHA was higher than primary AIHA, but it was not statistically different. SLE was the most common cause of secondary AIHA, which was prescribed on second-line drug as high as 64%. This could be explained by the fact that SLE patients had a high probability rate of relapse by disease nature and might also receive second-line treatment due to other organ involvement.

Commonly used second-line therapies in the present study were immunosuppressive drugs including cyclophosphamide and azathioprine, although there were...
limited numbers of studies to support the efficacy. However, the overall response rate from second-line treatments in the current study was higher at 93% than the 40–60% response rate of immunosuppressive drugs from the literature. High response rate in our study may be due to a high prevalence of steroid dependence and other indications for SLE, which trended to respond more than the relapse and steroid refractory group. Only two patients underwent splenectomy, which was accepted as effective second-line therapy for AIHA, since this is an invasive procedure and has some risks such as overwhelming infections. Rituximab has good activity in refractory severe AIHA with a response rate of 77% and is also recommended as second-line treatment. In the GIMEMA study, rituximab both standard dose (375 mg/m² per week for 4 weeks) and fixed low dose (100 mg per week for 4 weeks) was used as second-line therapy in 16 out of 123 patients (13%) with primary warm-type AIHA or 25.8% of patients who required second-line treatment. The frequency of rituximab therapy in the GIMEMA study was equal to splenectomy and about half of immunosuppressive therapy (24% of total cases and 48.4% of second-line treatment). By contrast, no patient in this study received this monoclonal antibody probably due to its high cost and not being approved for treatment of AIHA in Thailand.

In the present study, half of the patients relapsed especially primary AIHA and secondary AIHA from SLE but more than half of them occurred after 3 years of diagnosis. These findings were consistent with those previously reported that around half of AIHA patients had high risk of relapse. Interestingly, 44% received only corticosteroids without addition of second-line treatment and had good response. This supports the trial of increasing steroid dose for management of relapsed warm-type AIHA before shifting to second-line treatment.

The estimated 1 year OS of 89% was comparable to other studies. The majority cause of death was sepsis possibly because these patients took corticosteroids with or without other immunosuppressive drugs that could increase the risk of infections. Infectious complications were also reported as the common cause of death of AIHA patients in a French study, which was comparable with NHL (five from 83 patients both). Secondary AIHA from cancer and age more than 50 years were factors that predicted lower survival in this study. These findings illustrate the importance of cancer screening in AIHA patients.

The limitation of this study mainly was from its retrospective nature, which led to incomplete data, and some patients who were lost to follow-up or transferred to other hospitals. However, the present study provided overall clinical features, causes, and outcomes of warm-type AIHA patients in Thailand.

**Conclusion**

AIHA has a good prognosis and long-term survival especially in young patients without secondary malignancy. Most patients have responded initially to steroid treatment and have a high response rate to second-line therapy. The most common cause of death was sepsis, which was related to treatment side effects.

**Disclaimer statements**

**Contributors** E.R. wrote and revised the paper; P.E. collected and summarized clinical data, and wrote the paper; A.T. designed the research, obtained researched grant, analyzed data, and wrote the paper; and T.R., S.H., C.C., and L.N. revised the manuscript.

**Funding** This study was supported by a research grant from the Faculty of Medicine, Chiang Mai University.

**Conflict of interest** All of the authors declare no conflict of interest.

**Ethics approval** This study was approved by the ethical research committee, Faculty of Medicine, Chiang Mai University.

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