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AACR American Association for Cancer Research

Cancer Prevention Research

Analysis of DNA Methylation in Bowel Lavage Fluid for Detection of Colorectal Cancer

Taku Harada, Eiichiro Yamamoto, Hiro-o Yamano, et al.

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Current Topics
Paradigm Shift in Cancer
Research, Treatment
and Education

Juntendo Medical Journal
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Overview and Future Prospects of "Promotion Plan for the Platform of Human Resource Development for Cancer"

KOHZOH IMAI

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Overview and Future Prospects of "Promotion Plan for the Platform of Human Resource Development for Cancer"

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Promotion Plan for the Platform of Human Resource Development for Cancer (CancerHR Phase Two) had been launched in FY 2012. The newly selected five-year-project consists of 43 chairs in faculty of medicine: 9 chairs specialized in radiation treatment, 7 chairs specialized in chemotherapy, 10 chairs specialized in palliative care, and 17 other chairs. The above plans are expected to improve the platform of cancer education and research.

Key words: Promotion Plan for the Platform of Human Resource Development for Cancer, radiation treatment, palliative care, patient-oriented medical treatment

Human Resource Development Plan for Cancer (hereinafter referred to as CancerHR) was one of the educational projects established by Ministry of Education, Culture, Sports, Science and Technology in Japan (MEXT) in fiscal year 2007. The program had been highly evaluated so far.

Increasing the number of death from cancer having reached 350,000 a year, and increasing the awareness of cancer patients and their family which is represented by numerous Cancer Patient Meetings eventually brought it to enforce the Cancer Control Act. Based on such a background, CancerHR had been launched. I would like to describe my expectation for "Promotion Plan for the Platform of Human Resource Development for Cancer" (CancerHR Phase Two) started in FY 2012 since I have an opportunity to oversee the entire project as a Chairman of the Committee of Promotion of Human Resource Development for Cancer (Table-1).

CancerHR is a program for graduate student who specialized in clinical cancer, which has several features. First feature is that it aims to establish nationwide cancer treatment in cooperation with cancer medical treatment cooperation base hospitals. Second is that it aims to foster specialists, not only medical doctors but also nurses, pharmacists, and radiological medical physicist etc. In 4 years, the program achieved to foster more than 2,000 candidates (about 1,200 medical doctors) specialized in cancer. Third feature is that it placed great importance on radiation treatment, palliative care, and chemotherapy.

The research group of Ministry of Health, Labour and Welfare in Japan estimated that 2.25 million patients (diagnosed within 5 years) need cancer treatment in 2015. Although it seems like the actual number of cancer patients in need of treatment will go up to 4-5 million. Currently 15,000 "General Clinical Oncologists" who have the latest and comprehensive knowledge are certified (as of April 2014) despite 50,000 specialists are necessary. Further, only 514 Certified Nurses Specialist in cancer nursing and 2,684 Certified Nurses in cancer nursing are certified as of January 2014. These numbers are far from sufficient.

Having been launched recently, CancerHR started to achieve fostering cancer specialists. At

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Table-1 List of members of the Committee of Promotion of Human Resource Development for Cancer

	Shinsuke Amano	Executive Director of Group Nexus Japan, a nonprofit organization
Chairman	Kohzoh Imai	Director of Research Hospital, The institute of Medical Science, The University of Tokyo
	Hiroko Komatsu	Professor at Faculty of Nursing and Medical Care, Keio University
	Hiroshi Suzuki	Professor at The University Hospital, The University of Tokyo
	Nagara Tamaki	Director of Graduate School of Medicine, Hokkaido University
	Kazuo Tamura	Professor at Faculty of Medicine, Fukuoka University
	Satoru Tsuneto	Professor at a Corporate Sponsored Research Program in Graduate School of Medicine, Osaka University
	Keiichi Nakagawa	Associate Professor at The University of Tokyo Hospital
Vice chairman	Masahiko Nishiyama	Professor at Research Institute for Development Therapeutics, Saitama Medical University
	Okio Hino	Professor at Faculty of Medicine, Juntendo University
	Shigeri Hosaka	Executive Board Member of Japan Medical Association
	Mayumi Honda	Staff writer, Social Security News Department, The Yomiuri Shimbun

the same time it just started to collaborate between the specialists to make use of their professional skills, and universities and university hospitals had not been collaborated enough.

In view of the above, Promotion Plan for the Platform of Human Resource Development for Cancer (CancerHR Phase Two) had been launched in FY 2012 (Table-2). Based on the results and problems of Phase One, the following three results or effects are mainly picked up to make clear of target needs to proceed in Phase Two.

Construction of the cancer education research platform

Cancer education, research and medical treatment in Japan have been fallen far behind the international medical platform due to the separated operation in each of the internal organ specialties or medical specialties. This is because of insufficient cooperation between the internal organ specialties and medical specialties. Also the number of cross-disciplinary internal organ specialty chairs such as radiation treatment (separated from radiation diagnosis), chemotherapy (pharmacotherapy), and palliative care etc. are inadequate in number. Nevertheless, the newly selected five-year-project consists of 43 chairs: 9 chairs specialized in radiation treatment, 7 chairs specialized in chemotherapy, 10 chairs specialized in palliative care, and 17 other chairs. The above plans are expected to improve the platform of cancer education and research.

Promotion of cancer education reform

The project will accept 1,800 medical doctors specializing cancer treatment, and 1,200 medical personnel such as nurses and pharmacists in graduate school for 5 years. Other programs or education reforms are planned as follows:

1) In addition to educating cancer professionals in radiation treatment, chemotherapy, and palliative care, this project further set up a training course for surgical treatment, cancer treatment at home, pediatric cancer, gynecologic cancer, cancer rehabilitation, medical professionals, researcher and instructors who are involved in the latest and next-generation cancer research with the aim of extension of cancer professional education.
2) This project schedule to construct a new educational model to take advantage of characteristics of each university including a construction of e-Learning system, continuous interchange of personnel between local universities and universities in metropolitan area, programs applied to local networks having rooted in the area, programs principally aiming to team treatment, and education of researchers who are involved in the latest and next-generation research with the resource preserved in each university.

Table-2 List of Universities selected for Promotion Plan for the Platform of Human Resource Development for Cancer

Selected University	Name of Program	Number of Universities
Hokkaido University Asahikawa Medical University *Sapporo Medical University Health Sciences University of Hokkaido	Program of Human Resource Development for Leading Cancer Treatment in Hokkaido	4
*Tohoku University Yamagata University Fukushima Medical University Niigata University	Promotion Plan of Human Resource Development for Cancer in Tohoku	4
*University of Tsukuba Ibaraki Prefectural University of Health Sciences Dokkyo Medical University Gunma University Gunma Prefectural College of Health Sciences Saitama Medical University Chiba University Nippon Medical School	International Training Program for Co-operative Experts in Clinical Oncology	8
Jichi Medical University *The University of Tokyo Toho University Yokohama City University	Education Program for the Breakthrough in Cancer Treatment	4
Hirosaki University Akita University *Tokyo Medical and Dental University Tokyo Medical University Tokyo University Institute of Technology Tokyo University of Pharmacy and Life Sciences	Training Program for Next Generation Specialists to Promote Cancer Therapy	6
International University of Health and Welfare *Keio University Tokai University Tokyo Dental College Tokyo Metropolitan University St. Luke's International University Kitasato University St. Marianna University School of Medicine University of Yamanashi Shinshu University	Education Program for Professional Leader for Development in High-level Cancer Treatment	10
Iwate Medical University *Juntendo University Tokyo University of Science Meiji Pharmaceutical University Rikkyo University Tottori University Shimane University	Restoration Plan for Cancer Treatment through ICT and Human Resources	7
Kyorin University Teikyo University *Tokyo Women's Medical University Komazawa University	Tokyo Oncology Professional	4
University of Toyama *Kanazawa University Kanazawa Medical University Ishikawa Prefectural Nursing University University of Fukui	Hokuriku Training Program of Oncology Specialist	5
Gifu University Hamamatsu University School of Medicine *Nagoya University Nagoya City University Aichi Medical University Fujita Health University Meijo University	Education Program for Medical Professionals for Cancer Treatment between organizations	7
Mie University Shiga University of Medical Science *Kyoto University Kyoto Pharmaceutical University Osaka Medical College	Training Program for Next Generation Researchers and Medical Professionals Specialized in Cancer	5
Kyoto Prefectural University of Medicine *Osaka University Osaka University of Pharmaceutical Sciences University of Hyogo Kobe Pharmaceutical University Nara Medical University Wakayama Medical University	Human Resource Development Program for Cancer Coordinating Between Regions and Professions	7
Osaka City University Osaka Prefecture University Kansai Medical University *Kinki University Kobe University Hyogo College of Medicine Kobe City College of Nursing	7-University Joint Project: Advanced Creative Plan for Cancer Education Base	7
*Okayama University Kawasaki Medical School Hiroshima University Yamaguchi University The University of Tokushima Tokushima Bunri University Kagawa University Ehime University Kochi University University of Kochi	Mid-West Japan Cancer Professional Education Consortium	10
*Kyushu University Kurume University University of Occupational and Environmental Health, Japan Fukuoka University Fukuoka Prefectural University Saga University Nagasaki University Kumamoto University Oita University University of Miyazaki Kagoshima University University of the Ryukyus	Kyushu Promotion Plan for the Platform of Human Resource Development for Cancer	12

* University in charge of application
15 programs in total (100 universities)

Equal Accessibility to cancer treatment

Regardless of the residential area, patients should be able to access to cancer treatment of high quality based on a scientific knowledge (Equal Accessibility to cancer treatment). This project will foster cancer specialized professionals to work in those areas. The Following cases illustrate in detail.

1) This project is scheduled to open 83 courses to foster cancer professionals who will contribute the cancer treatment in local area, in which it will accept about 900 professionals in 5 years.
2) This project set up about 4 chairs specialized in local cancer medical cooperation such as local cancer treatment cooperation chair and local cancer treatment promotion chairs etc., in which it will promote to foster local oncologist, to construct local network, and to send oncologist to the local areas.
3) This project will open about 133 short-term learning courses (intensive courses) in graduate schools nationwide to accept about 3,000 professionals a year. This program enables the local medical professionals to learn the latest knowledge or treatment method of cancer preserved in universities.

Request from Committee of Promotion

Committee of Promotion requested the participating universities for the project as follows.

1) Conduct the plan accordingly as well as review to improve programs continuously to implement PDCA cycle with reference to an annual external evaluation conducted by external experts, comments from Committee of Promotion and social needs etc.
2) Return the result or effects to a society as much as possible and contribute the development of cancer treatment in Japan through educating excellent oncologists, and performing cutting-edge research and medical treatment for cancer.
3) Visualize the effort and effect as clear as possible to announce the public to recognize.

Committee of Promotion will continue to assess the progress of the project at interim evaluations and to support to enrich and develop the project.

Cancer control has been a critical issue for life and health of citizen in Japan thus Committee of Promotion requested the government to continue its financial support in which clearly stated on MEXT website.

As CancerHR Phase Two started, "National CancerHR Assembly" has been formally established by the universities selected for this program. The assembly is currently a private organization established with the aim to support programs at universities fostering cancer professionals involved in cancer treatment. Another objective of its establishment is to provide an occasion to exchange opinions of all universities belonged to the 15 main consortiums. Professor Nariaki Matsuura of Osaka University took the post as a Director. The Assembly held annual sectional meetings on palliative care in the first year (FY 2012), on radiation treatment in the second year (FY 2013), and will hold meeting on chemotherapy in the third year (FY 2014). Those meetings are available to exchange opinions of each university and to improve the program. Also some programs are open to general public to expand a patient-oriented medical treatment. All the above activities are in progress every year.

Japan has one of the highest life expectancy rates in the world, together with high incidence of cancer and death caused by cancer. Longer life results in increasing cancer for which the current situation would be regretful. Yet improvement of cancer treatment will improve the Quality of Life of patients and further bring vitality to a family, an office, and a community. The achievement of our country will greatly contribute many other countries with aging population around the world. This could be the grounds to launch "CancerHR Phase Three". Such successive CancerHR program will show a great value for cancer treatment and will foster personnel for contributing to cancer treatment worldwide in the future.

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ORIGINAL ARTICLE

Everyday clinical practice in IgG4-related dacryoadenitis and/or sialadenitis: Results from the SMART database

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Abstract

Objective. Immunoglobulin (Ig)G4-related disease (IgG4-RD) is a new disease entity that has only been identified this century. Clinical information is thus lacking. We established the Sapporo Medical University and Related Institutes Database for Investigation and Best Treatments of IgG4-related Disease (SMART) to clarify the clinical features of IgG4-RD and provide useful information for clinicians.

Methods. Participants comprised 122 patients with IgG4-related dacryoadenitis and/or sialadenitis (IgG4-DS), representing lacrimal and/or salivary lesions of IgG4-RD, followed-up in December 2013. We analyzed the sex ratio, mean age at onset, organ dysfunction, history or complications of malignancy, treatments, rate of clinical remission, and relapse.

Results. The sex ratio was roughly equal. Mean age at diagnosis was 59.0 years. Positron emission tomography revealed that the ratio of other organ involvements was 61.4%. Complications of malignancy were observed in 7.4% of cases. Glucocorticoid was used to treat 92.1% of cases, and the mean maintenance dose of prednisolone was 4.8 mg/day. Rituximab was added in three cases, and showed good steroid-sparing effect. The clinical remission rate was 73.8%, and the annual relapse rate was 11.5%. Half of the cases experienced relapses within 7 years of initial treatment.

Conclusion. We analyzed the clinical features and treatments of IgG4-DS using SMART, providing useful information for everyday clinical practice.

Keywords

Autoimmune pancreatitis, Cancer, IgG4-related disease, Mikulicz's disease, rituximab

History

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Immunoglobulin (Ig)G4-related disease (IgG4-RD) (see Supplementary Table 1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.950036) has recently attracted attention in many medical areas. IgG4-RD is characterized as a condition involving marked infiltration of IgG4-bearing plasmacytes and fibrosis in enlarged organs and elevated serum levels of IgG4 [1]. Organs that can be affected include the lacrimal and salivary glands, pancreas, bile duct, kidneys, lungs, pituitary gland, mammary glands, and prostate [2]. Until recently, lacrimal and salivary lesions in IgG4-RD have been called Mikulicz's disease (MD), and are now called "IgG4-related dacryoadenitis and sialadenitis" (IgG4-DS) [3]. In rheumatology and clinical immunology, IgG4-DS had been considered identical to Sjögren's syndrome (SS) [4], but has now been recognized as a separate pathological entity and differences from SS have been discussed [5].

A nationwide survey in Japan estimated that there were 8000 patients with IgG4-RD and 4300 patients with IgG4-DS [6]. With the growing awareness of this disease, rheumatologists have been identifying patients with IgG4-RD more often in daily practice, but information about the disorder remains unclear. We established the Sapporo Medical University and Related Institutes Database for Investigation and Best Treatments of IgG4-related Disease (SMART) to clarify the features of IgG4-DS and provide feedback on important and useful information for clinicians. We describe the results herein.

Materials and methods

Subjects were patients with IgG4-RDS diagnosed between April 1997 and December 2013 and currently under follow-up

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in our hospital or related facilities. All patients provided written informed consent and were registered to SMART. Patients who declined cohort participation or were lost to follow-up were excluded. Participants comprised all 122 patients with IgG4-DS who were registered to SMART as of December 2013. IgG4-DS was diagnosed according to the comprehensive diagnostic criteria for IgG4-RD [7] or the diagnostic criteria for IgG4-related MD [8], and we confirmed no Ig-heavy chain gene rearrangement. When Ig-heavy chain gene rearrangement was detected, we diagnosed B cell lymphoma. Patients encountered prior to the development of these criteria were diagnosed based on physical, serological, and pathological findings. The diagnoses of these patients were not changed during follow-up in any cases.

We analyzed the sex ratio, mean age at onset, distributions of age of onset, current age, involvement of organs other than the lacrimal and salivary glands as confirmed by positron emission tomography (PET) or computed tomography (CT), serum levels of IgG and IgG4 in patients with and without other organ involvement (OOI) as items prior to treatment, and treatments for IgG4-DS and adverse events, rate of clinical remission; MD assessment questionnaire (MAQ) scores (see Supplementary Figure 1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.950036) [9], relapse-free survival rate, and complications of malignancies as items during follow-up.

Systemic evaluation for complications of IgG4-RD and malignancies was performed using enhanced CT every year and ^{18}F-fluorodeoxyglucose (FDG)-PET at the diagnosis of IgG4-RD. If necessary, gastroenteroscopy or gynecological examination was added. Histological examination was performed to diagnose complications where possible. Physical and serological examinations were checked every 1–3 months. The MAQ comprises four questions to assess the degree to which lacrimal and salivary glands were enlarged and the occurrence and severity of sicca symptoms. Patients checked the boxes that best corresponded with current symptoms: disappearance of symptoms (0 points); slight improvement of symptoms (1 point); unchanged symptoms (2 points); or worsening of symptoms (3 points). The mean of these four questions was then used as the MAQ score, allowing comparison of patient condition compared with the first visit. Scores were checked at each visit. Clinical remission was defined as the disappearance of swollen lacrimal and/or salivary glands and no OOI by medical examination and imaging. Relapse was defined as re-enlargement of lacrimal and/or salivary glands or new/re-appearance of OOI after clinical remission.

In our treatment protocol, starting prednisolone at a dose of 0.6 mg/kg/day is considered appropriate for single-organ failure, increasing to 1.0 mg/kg/day with multiple-organ failure. However, the attending physician is permitted to decrease the initial dose due to age or physical complications. The initial dose of prednisolone is continued for 2–4 weeks, tapering the dose by 10% every 2 weeks. The attending physician can set a dose less than 10 mg/day. For relapsed or steroid-dependent cases, the dose of prednisolone is increased or concomitant use of immunosuppressants is selected (see Supplementary Figure 2 http://informahealthcare.com/doi/abs/10.3109/14397595.2014.950036).

Ethical considerations

Written consent to use case information was obtained from all patients prior to enrolment, in accordance with the Declaration of Helsinki. This study was conducted with the approval of Sapporo Medical University Hospital Institutional Review Board (SMU 22–57, 24-155).

Results

Smart

As of the end of December 2013, 122 patients with IgG4-DS had been enrolled. The mean follow-up period was 4.33 years, and SMART covered 528.81 person-years. Diagnoses for 76 patients were made according to the diagnostic criteria for IgG4-related MD, and all other patients met the comprehensive diagnostic criteria. Patients comprised 62 men and 60 women, representing a sex ratio of 1.03:1. Mean age at onset was 58.7 ± 12.6 years (range, 23–81 years), and the distributions of ages of onset are shown in Figure 1. The largest age stratum comprised patients in their 60s, and patients >60 years old comprised 56.6%. Mean (± standard deviation) current age was 64.5 ± 11.9 years.

OOI detected by PET

PET was performed in 70 patients before treatment. Involvement of organs other than the lacrimal and salivary glands was detected in 43 cases (61.4%). Organ failure excluding IgG4-DS was seen with one involvement in 27 cases (38.6%), two involvements in 8 cases (11.4%), and three or more lesions in 8 cases (11.4%) (Figure 2). Of these, 11 cases (15.7%) showed complications of type I autoimmune pancreatitis. Retroperitoneal fibrosis was seen in 14 cases (20.0%). Six of those 14 cases (42.9% of patients with retroperitoneal fibrosis) showed involvement of the renal hilum, and 3 of those 6 cases (50.0% of patients with lesions of the renal hilum) developed hydronephrosis. Soft tissues in the perivertebral space were observed in five cases (35.7% of patients with retroperitoneal fibrosis). Only two cases showed lesions around the ureter. Periaortitis was revealed in six cases. Lung involvement was detected in six cases (8.6%). Other lesions were detected in the prostate gland (nine cases, 12.9%), pericardium (three cases, 4.3%), thyroid gland (two cases, 2.9%), liver (two cases, 2.9%), and mammary glands (two cases, 2.9%). All cases of OOI described above were also confirmed with PET. In these 70 patients, OOI detected by CT alone were as follows: IgG4-related kidney disease in 16 cases (22.9%); and tracheal and bronchial lesions in 3 cases (4.3%). Involvement of the pituitary gland (one case, 1.4%) and seminal vesicles (one case, 1.4%) was detected only on magnetic resonance imaging (MRI).

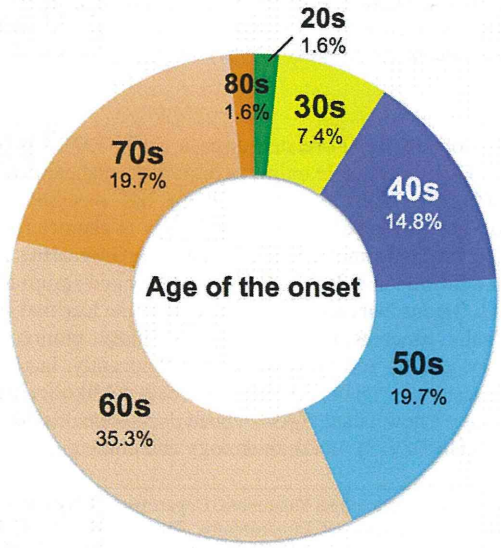

Figure 1. Distribution of age at onset in SMART. Patients over 60 years old comprised >55% of the database.

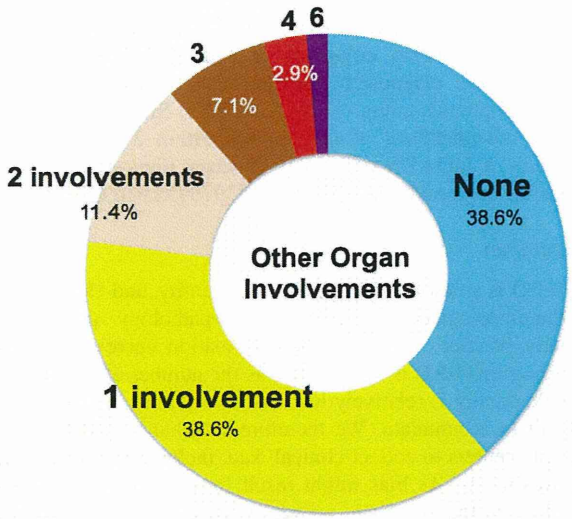

Figure 2. OOI by PET and CT evaluation. Involvement of organs other than the lacrimal and salivary glands was seen in 61.4% of IgG4-DS cases. More than three lesions were observed in about 11% of cases.

Serological evaluation at diagnosis

Sixty-nine patients (56.6%) with IgG4-DS showed hypergammaglobulinemia. Elevated levels of serum IgG4 and IgE were observed in 116 (95.1%) and 37 patients (30.3%), respectively. Hypocomplementemia was detected in 41 patients (33.6%). We divided patients into groups according to the presence or absence of OOI, and compared levels of these serological markers. The OOI-positive group comprised 75 patients (61.5%), and the OOI-negative group comprised 47 patients (38.5%). Mean levels of serum IgG were 2482 ± 1,351.1 mg/dL in the OOI-positive and 1872.5 ± 854.2 mg/dL in the OOI-negative group ($p < 0.01$). Mean serum IgG4 levels were 862.1 ± 714.8 mg/dL and 478.1 ± 363.3 mg/dL, respectively ($p < 0.001$). Levels of these markers differed significantly between groups (Figure 3); however, no significant difference was seen between groups in the proportions of patients presenting with abnormally elevated IgE levels or hypocomplementemia.

Maintenance treatment for IgG4-DS

Subjects in this analysis comprised 89 patients who presented with relapse in 2013, after excluding untreated patients and patients with tapering of glucocorticoid. Drug-free patients with clinical remission were included. The rate of glucocorticoid prescription was 92.1%, and the mean steroid dose for maintenance was 4.8 mg/day. Figure 4 shows the dose distribution. Patients treated with less than 5 mg/day of prednisolone comprised 52.8%, but some patients needed > 10 mg/day for the maintenance of clinical remission.

Immunosuppressants were used in combination with steroid for 9.0% of cases. The oral immunosuppressants used were azathioprine, and cyclosporine A. Rituximab was prescribed in three cases, each of which presented with several relapses (see Supplementary Table 2 http://informahealthcare.com/doi/abs/10.3109/14397595.2014.950036). The regimen comprised rituximab at only 500 mg/body every 6 months, with gradual extension of the intervals. The glucocorticoid-sparing effect seen as a reduction from 13.0 ± 2.7 mg/day to 3.7 ± 0.6 mg/day (-71.8%) using rituximab.

Clinical remission, relapse, and adverse events

An MAQ score of 0 was seen in 44.9% of patients (Figure 5) according to the analysis of patients treated with maintenance therapy. In all 122 patients, clinical remission had been reached and maintained in 73.8% of cases as of 2013. The rate of steroid discontinuation was 5.7%. Levels of serum IgG4 were still high (> 135 mg/dL) in some patients who achieved clinical remission, but levels of all serological markers (e.g., IgG, IgG4, IgE, and complements) were within normal ranges in all patients who achieved drug-free remission. The annual relapse rate was 11.5%. New OOI was seen in 28.6% of cases with recurrence. The mean dose of prednisolone at relapse was 3.2 ± 3.7 mg/day. A Kaplan–Meier relapse-free survival curve estimated that relapse occurred in half of patients within 7 years (Figure 6) using the data collected from April 1997 to December 2013.

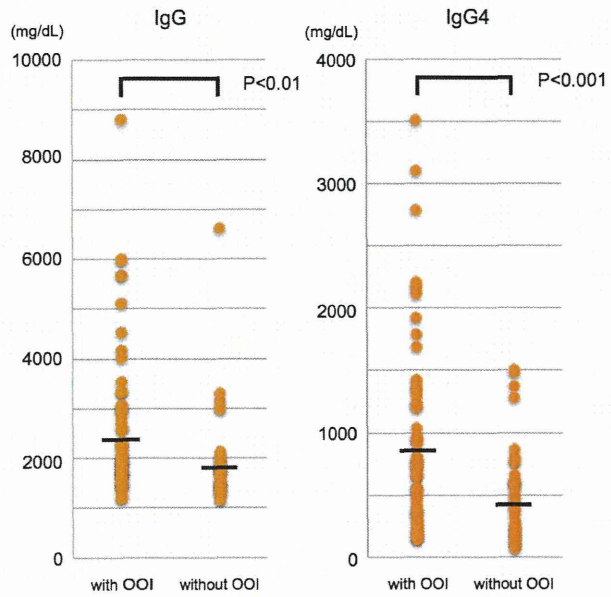

Figure 3. Levels of serum IgG and IgG4 in OOI-positive and -negative groups. The OOI-positive group showed significantly elevated levels of serum IgG and IgG4 compared to the OOI-negative group.

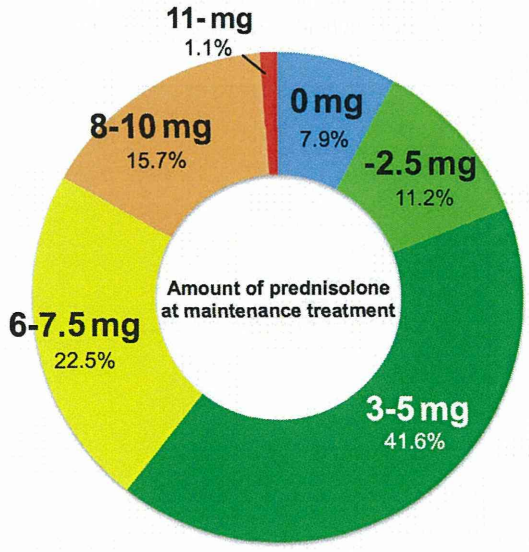

Figure 4. Dose of glucocorticoid for maintenance therapy. Mean steroid dose was about 5 mg/day. Control could be achieved on < 5 mg/day of prednisolone in about half of cases, but some required > 11 mg/day of steroids.

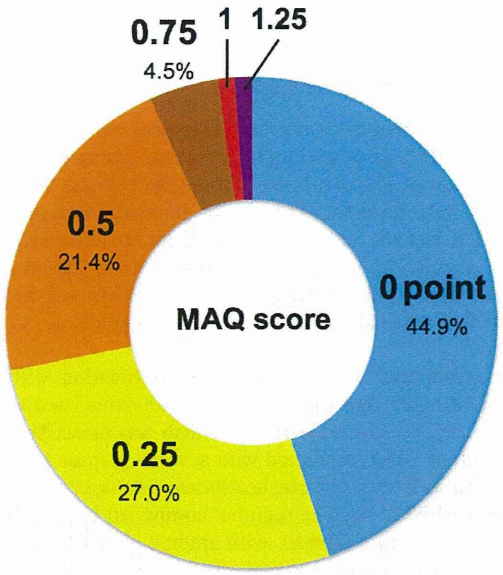

Figure 5. Distribution of MAQ scores. Only 44.9% of cases satisfied the criterion for improvement of clinical symptoms.

Severe adverse events were encountered in nine cases, comprising one case each of lymphoma, acute myeloid leukemia, sebaceous carcinoma, sepsis, pneumonia, and Mallory–Weiss syndrome, and three cases of osteonecrosis. Adverse events other than the above were observed in 13 cases, comprising 1 case each of suppurative osteomyelitis, scrotal edema, depression, angina pectoris, and umbilical hernia, and 4 cases each of herpes zoster and osteoporosis. The rate of adverse events was no higher in cases treated with immunosuppressants (including rituximab) than in cases treated using steroid monotherapy.

Complications of malignancy

On the other hand, the frequency of a history or complications of malignancy as of the end of 2013 was 7.4%, with lymphoma and breast cancer in two cases each, and acute promyelocytic leukemia, skin cancer, colon cancer, tongue cancer, and gastrointestinal stromal tumor (GIST) in one case each. Lymphoma comprised mucosa-associated lymphoid tissue (MALT) lymphoma and diffuse large B-cell lymphoma. PET was useful for detecting the cases with lymphoma, colon cancer, and GIST. Malignancy and IgG4-DS were diagnosed simultaneously in the patients with MALT lymphoma, colon cancer, and GIST. Six patients (66.7%) showed complications of malignancy within 3 years after the diagnosis of IgG4-DS (see Supplementary Figure 3 http://informahealthcare.com/doi/abs/10.3109/14397595.2014.950036).

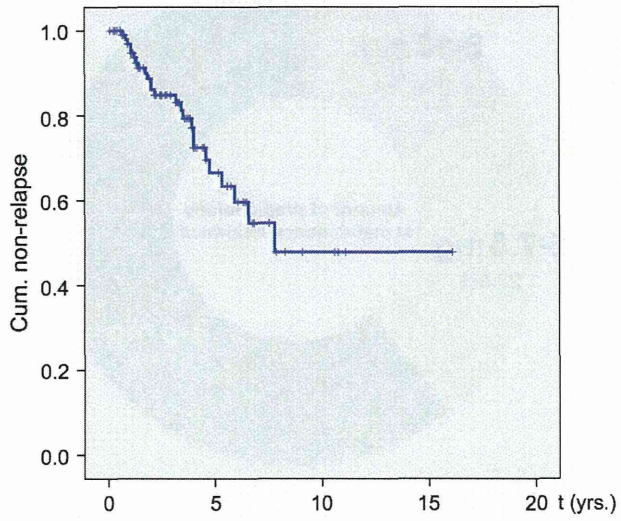

Figure 6. Kaplan–Meier relapse-free survival curve in IgG4-DS. The Kaplan–Meier survival curve showed that relapse occurred in about half of IgG4-DS patients within 7 years.

Discussion

IgG4-RD is a newly established disease entity, and the frequency of rheumatologists encountering this pathology is increasing in daily practice. However, the information currently available regarding IgG4-RD is insufficient, as the number of cases seen at a single facility is relatively low, and useful clinical data are thus difficult to accumulate. We therefore established SMART using multiple centers to collect clinical data, including patient profiles and treatments. As bias might result from us selecting cases to introduce to this database, we registered all cases from multiple facilities to eliminate the problem. This project will be continued into the future, and 122 patients had been registered to SMART and followed-up as of the end of 2013.

We have previously reported that patients with IgG4-DS, previously known as MD, were predominantly female [8]. The sex ratio recently seems to have shifted to either no bias or toward males with the gradual accumulation of cases, and is now close to the tendency seen with type I autoimmune pancreatitis [10]. The reason for this change remains unclear, but we believe that the data are getting closer to the correct sex ratio with the accumulation of IgG4-DS cases. The distribution of age at onset remains skewed toward patients over 60 years old, occupying about 60%. Considering IgG4-RD as a whole as showing a predilection toward older individuals might be appropriate. On the other hand, performing differential diagnosis for IgG4-DS using only the age at onset is not feasible, because the SMART showed some patients with IgG4-DS arising in their 20s.

Our study revealed that about 60% of cases with IgG4-DS showed the involvement of organs other than the lacrimal or salivary glands. This is a higher rate than expected, and involvement of more than two other organs comprised nearly 25%. IgG4-RD could be considered as a systemic disorder, and complications need to be evaluated systemically and carefully. We should recognize that these lesions are not necessarily single.

Next, we analyzed differences in serological markers compared to the first visit to identify factors predictive of OOI. Serum IgG and IgG4 levels were significantly higher in patients with OOI. No conclusion has been reached concerning whether these markers reflect the disease activity of IgG4-RD, but careful examination of whether high levels are present is important on the first visit. In daily practice, complications have to be checked for by routine use of contrast-enhanced CT and FDG-PET at diagnosis. Almost all patients in whom FDG-PET was not performed were experiencing economic hardships. Detection of organ involvement appears fairly straightforward. Several recent reports have described the utility of FDG-PET [11,12], but some organs are unsuited to the detection of lesions using FDG-PET, namely the kidneys and pituitary gland. Contrast-enhanced CT may overcome this weakness of FDG-PET if renal function is unhindered, but hypophysitis is difficult to detect on either FDG-PET or CT. We do not yet know the frequency of pituitary IgG4-RD. Whether MRI of the pituitary gland is needed as a routine screening examination on the first visit must be discussed. At present, we consider MRI as warranted when symptoms of pituitary hormone deficiency or pituitary gland compression are seen [13]. As described below, latent malignancies are an important problem in IgG4-RD. Only FDG-PET cannot differentiate between inflammation of IgG4-RD and malignancy,