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Financial risks posed by unproven cell interventions: Estimation of refunds from medical expense deductions in Japan

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Master et al. (2021) declared that the unproven stem cell intervention (SCI) industry is a global health problem and called for the establishment of a World Health Organization (WHO) expert advisory committee on regenerative medicine to tackle this issue beyond the efforts of individual countries. We fully agree with this opinion but would like to point out that there are financial risks in addition to the health risks they listed regarding unproven SCIs. The financial risks here do not refer to the problem of patients' paying high treatment costs for SCIs with unclear scientific evidence (although, of course, this is also a serious problem). Rather, the government (i.e., the public) bears part of the cost of the treatment through a tax refund system based on medical expense deductions.

Unproven stem cell therapies have been a global issue (Berger et al., 2016), and their number is especially growing in the United States, the largest market (Turner, 2021). Our research has focused on cell-based interventions and their regulation in Japan (Kashihara et al., 2016; Ikka et al., 2015; Fujita et al., 2016). Over the past few years, we found several websites of medical institutions in Japan that included sales messages explaining that cell-based interventions are eligible for "medical expense deduction." Medical expense deduction is a tax system in which the government pays a refund to compensate for the tax burden of people who must pay large amounts of the cost of a treatment. In Japan, annual medical expenses of 100,000 to 2,000,000 yen ($877 to $17,546 and €780 to €15,600, as of January 25, 2022) are deductible from the tax payment amount, allowing patients to receive refunds from the government. Medical expenses for both "health insurance treatment" covered by the universal health insurance system and "private practice" not covered by public insurance are eligible for deductions, although some medical treatments, such as cosmetic medicine, are excluded.

The Japanese national health insurance system currently covers treatments using regenerative medical products whose safety and efficacy have been confirmed by the government (such as cell sheets for serious heart failure and severe burns) in accordance with the Act on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals and Medical Devices (PMD act). Clinical trials demonstrating the safety and efficacy of regenerative medical products are conducted based on ICH-GCP (International Conference on Harmonization – Good Clinical Practice) guidelines. When treatment using such regenerative medical products is covered by health insurance, patients bear up to 30% of the total treatment costs, and 70% is paid by the government from insurance fees. Thus, insurance covers medical care that benefits many people.

Under private practice, cell-based interventions can be provided at medical institutions if certain procedures stipulated by the Act on the Safety of Regenerative Medicine (ASRM), such as making a provision plan that meets the implementation standards stipulated by law, which is then reviewed by a nationally certified committee, are complied with (Konomi et al., 2015). Because these cell-based interventions are not required to undergo clinical trials in general, many of them likely fall under "unproven SCI" rather than "treatment," according to the view of the International Society for Stem Cell Research (https://www.isscr.org/docs/default-source/all-isscr-guidelines/2021-guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation-2021.pdf?sfvrsn=979d58b1_4). Therefore, cell-based interventions can be provided without providing scientific evidence at the level required by the PMD act, which is regarded by some as a problem (Cyranoski, 2019). All costs of cell-based interventions offered under private practice are paid by patients at the moment.

Although these treatments are all considered cell therapies, there is a large difference in their contents offered under the health insurance system and in private practice. Nevertheless, the medical expenses required for these treatments are equally eligible for medical expense deductions. In other words, even for unproven treatments provided by a private practice, the patient does not have to bear the full cost. In this way, the government may subsidize the cost of a private practice cell-based treatment that is based on uncertain scientific evidence. In addition, the claim on some websites of these practices that a refund can be received

after the treatment may motivate patients to pursue the treatment.

Therefore, we estimated the total refund amount paid by the government for cell-based interventions offered under private practice in Japan, aiming to provide empirical data on the financial impact of cell-based interventions with uncertain scientific evidence on society (i.e., financial risk).

The ASRM aims at "reconstruction, repair, or formation of the structure or function of the human body" or "treatment or prevention of human diseases" and targets medical treatments using "cell processed products." The "processing" of cells refers to "performing drug treatment, modification of biological properties, and combination with non-cell components or genetic engineering modification for artificial proliferation and differentiation of cells and tissues, establishment of cell lines, and cell activation," excluding blood transfusions, hematopoietic stem cell transplantations, and assisted reproductive technologies. Therefore, in addition to stem cell-based interventions, the results below include cancer immunotherapy and platelet-rich plasma therapy. In this study, the treatments provided according to the ASRM are referred to as "cell-based interventions."

The refund amount paid to patients by the government indicates the amount of medical expense deduction (for annual medical expenses of 100,000 yen or more, a maximum of 2,000,000 yen is covered from the total medical expenses after subtracting 100,000 yen) multiplied by the income tax rate. However, because the amount of the medical expense deduction and income tax rate vary greatly from person to person, it is practically difficult to determine these two values individually. Therefore, we (1) estimated the mean amount of the medical expense deduction per case of approved cell-based intervention on the basis of documents published for patients by the Ministry of Health, Labour, and Welfare (MHLW) in Japan; (2) calculated the average income tax rate by prefecture on the basis of the information published by the Ministry of Internal Affairs and Communications; and (3) determined the average refund amount per case of cell-based intervention by prefecture on the basis of (1) and (2). By multiplying this average by the annual number of patients (or the number of injections; both published by the MHLW) by prefecture, we calculated the annual amount of refund for each prefecture and totaled the amounts to determine the total annual amount of refund for the whole country (see the supplemental information for details).

According to the information published by the MHLW, 37,911 people received a total of 70,810 cell-based interventions in 2017, and 67,407 people received a total of 113,550 cell-based interventions in 2018. Using the method described above, the total annual amount of medical expenses for cell-based interventions for the number of patients was estimated as 1.0 billion to 79.5 billion yen (median 7.1 billion yen) in 2017 and 1.8 billion to 141.4 billion yen (median 12.7 billion yen) in 2018. On the basis of the number of injections, the estimated amount was 1.9 billion to 148.5 billion yen (median 13.3 billion yen) in 2017 and 3.0 billion to 238.2 billion yen (median 21.3 billion yen) in 2018. The total annual amount of refund for the number of patients was estimated to be 105.4 million to 8.2 billion yen (median 881.6 million yen) in 2017 and 191.3 million to 14.9 billion yen (median 1.6 billion yen) in 2018. On the basis of the number of injections, the estimated amount was 201.9 million to 15.8 billion yen (median 1.7 billion yen) in 2017 and 325.7 million to 238.2 billion yen (median 2.7 billion yen) in 2018 (see Table S5 in the supplemental information for the respective amounts converted to US dollars and euros).

We recognize that this survey estimated only the costs and number of treatments on the basis of the materials published by the government. In addition, not all patients apply for the medical expense deduction. These facts must be considered when interpreting the results of this survey.

Nevertheless, our findings estimate that the total refund amount for private practice cell-based interventions, including unproven SCIs, is in the hundreds of millions of yen per year. Thus, a substantial amount of public funds—not only as treatment costs paid by the patients but also as taxes—is spent even on treatments with uncertain scientific evidence. In other words, financial risks posed by unproven cell-based interventions, particularly SCIs, are not only private issues for patients but also public issues. Although revisions to the ASRM are currently being discussed (Takashima et al., 2021), the estimates in this study argue that serious consideration be given to whether the ASRM should continue to allow the provision of unproven cell-based interventions. Moreover, it is likely similar financial risk exists in other countries as well. In fact, private practices in other countries highlight similar deductions (Turner, 2018). Investigations and reports from other countries are needed to determine whether those countries too are incurring similar financial risks for unproven cell-based interventions, especially SCIs.

WEB RESOURCES

ISSCR Guidelines for Stem Cell Research and Clinical Translation, https://www.isscr.org/docs/default-source/all-isscr-guidelines/2021-guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation-2021.pdf?sfvrsn=979d58b1_4

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.stemcr.2022.03.015.

AUTHOR CONTRIBUTIONS

T.I. conceived the study. T.H. designed the equations to implement the ideas and collected and analyzed the data with K.I. M.F. supervised the process from the equation design to the analysis. All authors contributed to the data interpretation, participated in discussions on important intellectual content, wrote the manuscript, and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no competing interests.

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