



Patients' Reimbursement Trade-offs for Radioactive Iodine-Refractory Differentiated Thyroid Cancer Treatments are Simulated by Mushroom Cementation of Bio - based products from Microbial degradation of Radioactive Cellulosic-Based Material

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Abstract

In the current study, solidification of bioproducts produced by the bioremediation of a combination of radioactive waste made of solid cellulose was investigated in Portland cement. After 28 and 90 days of cure, the resultant solidified waste form was evaluated for mechanical integrity. Over the course of 540 days, the chemical performance of the cement-waste form was also assessed in various leaching media. The collected provided useful information regarding the final cement-waste form that contained the radioactive bioproducts in terms of its mechanical, physical, and chemical capabilities. Additionally, it revealed that cement can operate as a first line of defence against the release of radioactive pollutants from radioactive wastes to the environment and can offer a highly durable form that ensures the long-term stability of the solidified waste material.

The purpose of this study was to evaluate patients' preferences for when to begin systemic therapy and how to help them decide whether to trade off certain severe adverse events (AEs) for additional progression-free survival months (PFS). Materials and Techniques A direct-elicitation question and a discrete-choice experiment (DCE) were completed online by adults in France, Germany, and Spain who have been diagnosed with DTC and have received at least one RAI therapy. Respondents were asked if they would choose not to get treatment if their tumour was RAI-R in a direct-elicitation question. Respondents had 12 pairs of fictitious RAI-R DTC treatment profiles to select from in the DCE. Dimensions of effectiveness (PFS) and safety served as the benchmarks for profiling (severe hand-foot skin reaction [HFSR], severe proteinuria, and severe hypertension). The estimated logit model used main-effects random-parameters. The survey had 134 patients respond. Eighty-six percent of patients chose therapy over a "wait and see" strategy. Compared to the risks of proteinuria and HFSR, patients gave more weight to the risk of severe hypertension. In contrast to watchful waiting, DTC patients preferred therapy for RAI-R DTC. Severe proteinuria or HFSR seems to have less of an impact on patients' decisions than their worries about the possibility of developing severe hypertension.

Keywords: Hypertension; Tumour; Radioactive waste

Introduction

For the future utilisation of the benefits of nuclear technology in both energy-related and non-energy-related domains, the problem of the radioactive wastes produced by non-nuclear radioisotope applications around the world is of the utmost importance.

The ability of living organisms to biodegrade, bio absorb, bioconcentrate, and bio stabilize the radionuclides from the contaminated waste together with a contemporaneous reduction in its volume is the foundation of the novel technique known as "bioremediation" for solid cellulose-based radioactive waste [1]. This procedure has been the subject of research for more than 10 years at our lab, where it has been used to treat a variety of liquid and solid radioactive waste models.

A mushroom has been used to remediate solid cellulose-based radioactive waste samples (such as a combination of contaminated protective clothing, damaged cotton, and used tissue and filter paper). The remaining bioproducts, including the fungus that is developing and the portion of the compost that has not yet disintegrated, have been immobilised in Portland cement (PC). The produced solidified waste form is intended to be safely disposed of or kept for extended periods in a designated repository away from people and their surroundings. Although cement has a number of drawbacks as a matrix for solidification, including low volume reduction and relatively high leachability, it also has a number of advantages in real-world

applications, including good mechanical integrity, low cost, and eases of use, in addition to radiation and thermal stabilities.

To determine if PC is suitable for waste fixation during the encapsulation of bioproducts produced by the bioremediation of cellulose-based waste simulators, preliminary experiments were carried out. Forms made of cement and trash was created using various ratios of cement paste to bioproducts. To assess the integrity of the mechanical system, their compressive strengths were measured. Following the procedure advised by the International Atomic Energy Agency, a leaching test for the cement-waste forms was performed for more than 500 days of immersion [2]. Calculations were made for the ^{137}Cs and ^{60}Co released from the cemented waste form during the leach test, including the incremental leach rate (R_n), diffusion

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coefficient (De), and leach index (Lx).

Thyroid cancer makes up 2.1% of all new cancer cases worldwide. Nearly 94 percent of thyroid tumours are differentiated thyroid cancers (DTC), which include papillary, follicular, and Hurtle cell types. The three main therapy modalities for DTC are thyroid-stimulating hormone suppression, radioactive iodine ablation, and surgical excision. With an 85% 10-year disease-specific survival rate, the prognosis for DTC is excellent overall. A 10-year disease-specific survival rate of 40% is seen in patients who acquire distant metastases, which affect 10–15 percent of patients [3]. However, the ability to absorb RAI is lost in certain DTC patients who acquire metastases, with a 10-year disease-specific survival rate of 10%. On the optimal way to describe RAI-R DTC, agreement is growing. In patients with advanced disease, it is indicated by the presence of at least one tumour focus without any RAI uptake, the progression of the disease during the year following a course of RAI treatment, or the persistence of the disease following the administration of a cumulative dose of 22 GBq radioiodine. In light of the fact that not all patients with RAI-R DTC have disease-related symptoms at progression, doctors must decide when to begin treatment. Poor outcomes and shaky evidentiary support have been the norm when treating RAI-R DTC with conventional chemotherapy drugs like doxorubicin.

Identification of intracellular mechanisms associated in the pathophysiology of DTC has been the subject of research. Tyrosine kinase inhibitors (TKIs) and angiogenesis pathways are two molecular targets that are currently in the spotlight. Lenvatinib and sorafenib were recently licenced for the treatment of RAI-R DTC on the basis of successful randomised clinical trials [4]. Physicians find it challenging to choose between these two systemic medications because there is currently no study that compares these two approved medicines head-to-head. For RAI-R DTC patients, there are no published studies that assess patient preferences for particular course of treatment.

The purpose of this study was to determine how patients would trade off extra months of progression-free survival (PFS) with specific severe adverse events that differ between the two approved systemic treatments. It also sought to determine how patients would decide whether to wait or begin systemic treatment. The idea is that patients weigh long-term side effects with unknown consequences more heavily than short-term side effects that can in a decline in quality of life when deciding which treatments to pursue.

Materials and Methods

Materials

Cement was used to immobilise the bioproducts created by the mushroom *Pleurotus pulmonarius*' biodegradation of a mixture of cellulose-based wastes (equal parts protective clothing, cotton, and paper). The combination made of cellulose was analysed chemically.

The biodegradation of radioactively contaminated composts was carried out, the resulting spiking bioproducts were immobilised in cement matrix, and the specimens were then subjected to chemical testing. Before growing the mushroom, contaminants such cesium-137 (137Cs, $t_{1/2} = 30$ years) and cobalt-60 (60Co, $t_{1/2} = 5.27$ years) were added to the substrate [5]. The two gamma emitter radionuclides (137Cs and 60Co) were bought from Amersham, England. The ability of the cement-waste form to endure the repository conditions was assessed in this work using three different leaching media: tap water, groundwater, and seawater. The concentration of some relevant ions in these various mediums.

Methodology

After being air-dried and then placed in an oven at around 50°C to stabilise its weight, the bioproduct created by bioprocessing a combination of solid cellulose-based waste to resemble a mushroom was packaged. Before being included into the cement matrix, these bioproducts were pulverised in a metallic grinder. The bioproducts and cement paste were compared in five different ratios (i.e., from 1 to 5 percent by weight). By combining cement powder and water at a 0.35 water/cement ratio, cement paste was created. It should be noted that the bioproducts should first be thoroughly wetted with water before being combined with the cement paste. After being manually compressed for the specified amount of time and put into cylindrical moulds, the entire cement-waste mixture was mixed.

These moulds were wrapped with polyethylene and allowed to cure at ambient temperature (25 °C) in the humid environment. After 28 or 90 days, solid blocks were demolded before a mechanical test was performed on them. Utilizing the Ma test and the E-159 sp apparatus, the compressive strength of three to five specimens of cement waste measuring 60 mm in height and 31 mm in diameter was evaluated [6].

Spiked solid cement-waste form blocks were made by combining cement paste with a cement product at a weight-to-volume ratio of 0.35 and a bioproduct at a rate of 2% by weight in order to assess the chemical characterization. After 28 days of drying, the 137Cs, 60Co, or both contaminated blocks were hung up in plastic jars with at least 10 mm of lead in each direction around the sample. The three immersion media—tap water, groundwater, or seawater—were each used in one of the jars.

Using a 3 inch NaI well-type crystal, a multichannel analyzer, and the PCAP programme, the radioactivity in various leaching media was counted [7]. The radioactivity's incremental leach rate (Rn), diffusion coefficient (De), and leach index (Lx) were then calculated for the cement-waste forms at different leaching times (USA). After the setting and curing times, IR analysis was done on the bioproduct, plain cement, and cement-waste forms to track the immobilised bioproducts that came from the bioremediation process. IR spectra were measured with the help of (Perkin-Elmer spectrum RX IFTIR system). The specimens were made by combining 200 mg of KBr and 1 mg of the material as a powder (AR grade). A spectral study with a spectral resolution of 1 cm⁻¹ was conducted in the 4000-400 cm⁻¹ region.

Preference-Elicitation Questions

In order to determine patient preferences for RAI-R DTC therapies, we followed best practises for creating and implementing a discrete-choice experiment. This approach has been widely used in the field of health and is based on both psychology and economics. Online surveys have been used in a number of DCE studies in oncology to assess patient treatment choices. Respondents to DCE research are asked to select one of several fictitious treatment options in response to a series of multiple-choice questions. The extent to which different treatment qualities are satisfied by treatment alternatives defines them. The treatment profiles produced by the systematic variation of the attribute values across the multiple-choice questions are not indicative of any existent treatment.

The relative relevance of a given treatment is determined by performing a multinomial regression analysis on the respondents' selections and determining how the attribute levels provided affect that treatment's importance. A direct-elicitation question asking respondents if they would refuse treatment if their tumour had RAI-R was included in the series of choice questions [8]. The percentage

of respondents who would agree to beginning any of the therapies suggested in the direct-elicitation question represents the respondents' preferences for the kind of treatments they would like to receive.

Survey Instrument

We analysed package inserts and phase 3 clinical trial data of recently authorised systemic medications to identify the four qualities and corresponding levels for the choice questions. The risk of a severe hand-foot skin reaction, a severe proteinuria, and a severe hypertension were three primary safety measures that we included along with a main efficacy measure. Using the phase 3 clinical trial data for the two approved TKIs as a guide, the three severe AEs were picked because they had the biggest variation in incidence rates. The levels for each attribute were created to cover the range seen in clinical trials and the range over which respondents were willing to make trade-offs between the four attributes. A nontechnical language was used to define each attribute.

Statistical Analysis

With the help of a random-parameters logit model, responses to the choice questions were examined. The attribute levels served as explanatory variables, and the treatment selection served as the dependent variable. Nonlinear effects were roughly represented by higher-order polynomial components in the model with continuous variables. With the aid of specification tests, it was discovered that preferences for PFS and severe hypertension improvements changed nonlinearly and were represented using quadratic and linear terms. Accordingly, depending on the starting point of that improvement, a one-unit change in any of these two traits could have a distinct effect on preferences. The estimations of the parameters that quantified the relative weight or strength of liking for each level of an attribute. Using NLOGIT 4.0, all analyses were performed (Econometric Software, Inc., Plainview, New York, USA).

Results

Portland cement was chosen as an immobilising matrix because to its many benefits, including its ease of use, low cost, and good mechanical and thermal stability. The backing of a safety evaluation often serves as proof of the long-term security of facilities for disposing of radioactive waste. The standards that were met by the waste forms in terms of mechanical, chemical, physical, and other factors are one of the factors defining the safety of the entire radioactive waste management plan.

Patients Sample Characteristics

Out of the 162 patients invited, 144 accepted the invitation, and 141 qualified. A sample size commensurate with current DCE practises in health was selected from among the eligible respondents, with 134 (response rate = 82.7%) giving informed consent and being included in the study. The final sample's demographics were as follows: 84% of the participants were female, 78% of them were married, 58% of them held a job, 87% of them had papillary thyroid cancer, and 68% had received their diagnosis at least two years prior. The average age (standard deviation [SD]) was 47.2 (12.5) years. Although there was no information on the severity of this health issue or if it was related to DTC drugs, nearly 20 percent of the sample (19.4 percent) reported having high blood pressure. 8.2 percent of the patients who answered the poll said they were.

Patient Preferences

Any attribute's total relative importance can be calculated by

measuring the vertical distance between the preference weights for its greatest and worst levels. According to respondents, improving PFS from 6 months to 24 months was the most crucial attribute out of all the traits and levels included in the poll. The importance of improving PFS by 18 months was around 0.86 times greater than reducing the treatment-related risk of severe hypertension from 50% to none. It was roughly equivalently essential to reduce the treatment-related risk of severe HFSR from 20% to 0% as it was to reduce the risk of severe proteinuria from 10% to 0%; these modifications were around 0.24 times and 0.25 times as significant as increasing PFS by 18 months, respectively the three extremely dangerous AEs.

Discussion

Every calcium-containing phase that exists in cement is subjected to carbonation, with Ca (OH)₂ being the more quickly reacting substance. Calcium carbonate, silica gel, and metallic oxides are produced as a reaction, and when they aggregate and obstruct the pores of the final waste form, the mechanical integrity of the waste becomes more robust. Based on the information from the mechanical integrity measurements, it is possible to conclude that the final cemented waste form, which contains up to 5% of the bioproduct by weight from the bioremediation of cellulose-based waste, can satisfy the requirements for secure handling, transportation, interim storage, and final subsequent disposal.

Three key findings from our investigation, together with their clinical repercussions, were presented. Given the trade-offs presented in the direct-elicitation question, DTC patients first indicated a preference for RAI-R DTC treatment over careful waiting. Since a scenario, 86.6 percent of patients chose to begin therapy rather than "wait and see," as they realised that if DTC develops to RAI-R, it is no longer a slow-moving disease. Being RAI-R DTC, on the other hand, typically indicates that the patient has undergone a lot of prior and ultimately unsuccessful treatments. This may influence the decision to begin a new treatment when they may monitor the reaction of their disease in response to treatment.

The aim of our study also showed that patients weighed the four RAI-R DTC therapies' treatment-related advantages and disadvantages when deciding which one to get. Due to the lack of information on patient treatment preferences at this time, this contributes to the body of research in RAI-R DTC. In shared decision-making between patients and doctors, patient viewpoints can be taken into account. Studies like this one can also give patients some insight into the pros and cons of treatment versus a "wait and see" choice. Third, PFS improvement was rated as the most significant attribute by patients. In contrast to the modifications included for the risks of severe proteinuria or severe HFSR, patients' worries about the risk changes included in this analysis for severe hypertension appear to have had a higher influence on patients' choice of treatment. Potential explanations for this finding can be found in the face-to-face interviews, where patients expressed greater concern for AEs that did not cause immediate symptoms but might cause grave sequelae, such as potentially fatal cardiac events brought on by chronic hypertension or renal impairment brought on by proteinuria. It's possible that patients were worried that these AEs could need ongoing monitoring in long-term health issues. Although annoying and unpleasant, HFSR onset is DCE research has limitations, while being used in health applications at an increasing rate. First, respondents assess hypothetical therapies; despite the fact that the trade-offs are meant to imitate potential therapeutic judgments, they do not have the same clinical, monetary, or emotional repercussions as real ones. There may be discrepancies between claimed and real

therapy options. Second, this study solely compared specific adverse events (AEs) between the two approved systemic treatments. This study may not have taken into consideration all of the variables that could affect how people choose their treatments.

Third, the study's sampling plan makes it less certain that these findings can be extrapolated to the community of RAI-R DTC patients. For instance, we carried out a convenience survey among online DTC patients in France, Germany, and Spain. When compared to the real patient groups in the clinical trials, our sample was younger and comprised more women. A portion of the patients who took part in this trial did not have prior knowledge of RAI-R disease and would not have been exposed to the hazards associated with the three AEs that were studied because only 8.2 percent of RAI-R DTC patients in our sample had the condition. Although the power of our study did not allow us to compare the preferences of different subgroups often generalise our findings to patients with different demographics or treatment histories, or to patients in other European nations or beyond, would be risky. For instance, the finding that severe hypertension was more significant than severe proteinuria or severe HFSR and that PFS was the most significant attribute may have a different effect on an older sample of actual RAI-R DTC patients who may have other comorbidities and who are better able to comprehend the effects of comorbidities like severe hypertension in their lives. It would be especially beneficial for future studies to confirm our findings utilising a randomised patient sample receiving TKIs for RAI-R DTC.

In contrast to watchful waiting, DTC patients preferred therapy for RAI-R DTC. Patients' worries about the possibility of developing severe hypertension seemed to have a bigger influence on their decision to get systemic therapy than worries about having severe proteinuria or having severe HFSR. The findings of this study may help patients and doctors make informed decisions about RAI-R DTC treatments by providing some understanding of patients' perspectives on treatments.

Conclusion

Methane may not be the terminal gas if the acidity produced by the microbial breakdown of cellulose is not appropriately buffered to a pH above 6, according to long-term pressure monitoring of sealed containers and periodic examination of the headspace gas composition. We need to replicate our findings using different trash kinds in order to support our findings. While waiting, measuring the amount of cellulose in low-level waste is necessary before projecting gas generation within a DGR safety situation. Then, an assessment of the localised buffering capability of the cement and host rock is required, along with a prediction of the acid formation from cellulose degradation [9]. The biodegradation of cellulosic material involves numerous processes and is rate-limited by the early breakdown of solid cellulose, which complicates the prediction of acid formation.

By excavating geological repositories several hundred metres below the surface, the degree of degradation of naturally occurring and artificial barriers brought on by the production of acidity would stay limited. Repositories located at significant depths offer isolation and an additional margin of safety to balance the risks connected with the effect of acidity on naturally occurring and artificial barriers [10]. The dose to the public and the environment must also be shown to be acceptable for hundreds of thousands of years, or until the radioactive stockpile decays to background levels, even if the shaft seal material of DGRs is badly deteriorated by any factor, including acidity.

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Conflict of Interest

The author has no known conflict of interest associated with this paper.

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