

COMMENTARY

High-dose I-131 therapy on outpatient basis: imperative and no more a desire

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Abstract

Iodine-131 (I-131) ablation of thyroid cancer with more than 30 mCi dose is instituted on inpatient basis in most of countries as per local statutory requirements. The basic reason for the internment is to avoid possible risk of radiation exposure to the caregivers and the public, from the patients treated on an outpatient basis. There is no doubt that isolation causes significant financial stress and has a negative psychological impact on patients. In 1997 (and revised in 2009), Nuclear Regulatory Commission (NRC) of United States allowed the licensees to release patients after high doses of I-131 with verbal and written instructions to be follow at home. Various studies from different part of the world have shown that radiation exposure to caregivers and public from patients treated with high doses of I-131 on an outpatient basis, were well below the statutory limit (<5 mSv/year). Furthermore, a recent study from Japan has revealed high mortality in patients who had delayed I-131 treatment for one reason or other. In this commentary we have elucidated the basic facts about the radiation exposure to public and caregivers resulting from outpatient I-131 treatment and also briefly discuss the feasibility of high-dose I-131 treatment in Pakistan.

***Key words**: I-131, outpatient, thyroid cancer, radiation exposure, ALARA*

Introduction

Iodine-131 (^{131}I) is used for the ablation of post surgical thyroid remnants or treatment of iodine avid recurrent and/or metastatic thyroid lesions, with reduction in recurrence and possibly in mortality rates [1]. ^{131}I is a reactor produced isotope, having a physical half life of about 8 days and emits gamma rays of 364 KeV and beta particles (maximum energy 0.6 MeV). It has been used for the last six decades. Radiation exposure from a treated patient to a caregiver, household or a member of public has been a major concern. Meager data on effective dose exposure to others and misinterpretation of International Atomic Energy Agency (IAEA) and International Commission on Radiological Protection (ICRP) recommendations, have paved the path for in-patient treatment of all medical procedures involving ^{131}I activities higher than 30 mCi globally [1]. However, in 1997, the Nuclear Regulatory Commission

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(NRC) of United States (US) amended 10 CFR 35.75 (revised in 2009 also) which allows NRC licensees to release patients treated with larger doses of ^{131}I from their facilities under certain conditions (as out-patient) [1].

We believe we can modify the current practice and initiate high-dose outpatient radioiodine therapy in Pakistan, at least as a pilot project. This commentary explains the basic facts revolving around ^{131}I therapy on outpatient basis and briefly discusses its feasibility in Pakistan.

Iodine-131

Iodine-131 (^{131}I) is a reactor produced isotope, which has a physical half life of 8 days and emits high energy gamma rays and beta particles. About 90% of radiation dose delivered to the patient is caused by beta particles (maximum energy 0.6 MeV), while gamma rays (364 KeV) are responsible for remaining 10% of the delivered dose. Radiation exposure from a treated patient to the caregivers and public, is mainly caused by gamma rays and also by beta particles in case of surface contamination or accidental ingestion.

In patients treated for hyperthyroidism with thyroid uptake more than 50%, the effective half-life of ^{131}I is considered 5 days [1]. However, patients with thyroid cancer with total thyroidectomy usually receive larger initial ^{131}I activities, but retention declines more rapidly through urinary excretion, and especially when euthyroid patients are prepared for treatment with recombinant human TSH (rhTSH) rather than by hormone withdrawal [2]. In these patients, the effective half-life of ^{131}I during the first 8 hours (pre-equilibrium period) is considered constant (although some inter-patient variability exists) and is estimated to be 0.8 times the physical half-life, or 6.43 days [3]. After the pre-equilibrium period, the remaining ^{131}I is considered to be divided between the thyroidal and the extra-thyroidal components with effective half-lives of 7.3 and 0.32 days respectively [4, 5]. The majority of non-thyroidal ^{131}I is cleared biologically through urine in the first 48 hours and minority is eliminated via saliva, faeces and perspiration [6].

Radiation exposure to caregivers and public

The magnitude of radiation exposure from an ^{131}I-treated patient to a caregiver, a family member or a member of the public, depends upon: 1) retained radioactivity (resulting from residual functioning thyroid tissue in the body, administered radioactivity, patient's hydration and renal function), 2) distance from the patient, and 3) duration of exposure [8]. The estimated dose rate calculated by using the dose equation is 0.17 mrem/hr/mCi of ^{131}I at 1 meter distance [9]. Internal contamination of a caregiver or a family member of a treated patient is possible, and the possibility is highest in first 2-3 days. Patients should be instructed on what constitutes internal contamination and how to prevent it during the first 2 or 3 days after treatment [9].

The calculations based on mathematical models have inferred that the Total Effective Dose Equivalent (TEDE) to a person from a patient treated with 150 mCi of ^{131}I for carcinoma of the thyroid is 4.86 mSv (0.486 rem) or 3.40 mSv (0.340 rem) respectively. This is below the recommended dose limit (5 mSv/year) to a caregiver or public member from a patient treated with ^{131}I as per 10 CFR 35.75 (code of federal regulation) and is one of the basic facts fostering the administration of high-dose ^{131}I on outpatient basis [4].

Release of patients after ^{131}I treatment

High doses and high radiation dose rates (100 mSv to 1000 mSv) over a short period of time, are associated with various malignancies. Currently, there is no data that unequivocally establishes the occurrence of cancer following exposure to low doses or dose rates (e.g., below about 100 mSv). However, there is ample scientific evidence indicating that low-dose radiation (less than 100 mSv) does not produce significant damage to the exposed cells and that the health risks from annual

cells [8] and that the health risks from annual doses below 100 mSv are either too slight to be observed or nonexistent [9-13]. Average annual radiation exposure to an individual in the United States from natural and artificial (medical, commercial, and industrial activities) sources is approximately 3.6 mSv (3 mSv from natural and 0.6 mSv from artificial sources) [14]. No adverse health effects have been demonstrated from these levels of natural radiation exposure. Similarly, residents of areas with high levels of background radiation (>10 mSv/ year) such as Denver, Colorado, have shown no adverse biological effects [11].

On the other hand, by extrapolation with a linear no-threshold dose-response relationship between radiation and its biological effect, one may assume that exposure to low levels of radiation might result in some harm. This theoretical possibility of increased harm at any increase of radiation exposure beyond background radiation, combined with no evidence of benefit of radiation exposure to the public, has led to the practice of keeping radiation exposure to others As Low As Reasonably Achievable (ALARA) [11].

These theoretical risks and perhaps also some misinterpretation of International Atomic Energy Agency (IAEA) and International Commission on Radiological Protection (ICRP) recommendations have paved the way for government authorities to decree that all medical procedures involving ^{131}I activities higher than 30 mCi, must be performed on an inpatient basis [2, 15, 16]. However, clinical practice and protocols differ from one country to another, especially the duration of internment after which the patient can be allowed to leave hospital following treatment. The most stringent criteria are applied in Germany where the patient is required to have an activity less than or equal to 2 mCi on discharge whilst in United Kingdom, France, Belgium and The Netherlands, the maximum permissible radioactivity for ambulatory treatment with ^{131}I is between 10-20 mCi [21].

In the US before 1997, according to the NRC recommendations, every patient treated with >33 mCi of ^{131}I had to be admitted in an isolation room until the residual activity fell below 33 mCi or when the dose rate became less than 7 mrem/hour at 1 meter distance from patient [4]. The sentinel reason for this approach was to keep the radiation dose limit to the general public or care givers at <1 mSv/year. However, in May 1997 and updated in July 2009, NRC revised Code of Federal Regulation 10 CFR 35.75, which permits NRC licensed facilities to release a patient treated with ^{131}I from their control as long as the radiation exposure to a family member or caregiver will likely not to exceed 5 mSv (500 mrem) per year, and the radiation dose to a child, a pregnant woman or an individual not involved in the care of the patient, will not exceed 1 mSv (100 mrem) per year. If either of these limits may be exceeded, then the released patient must be provided with verbal and written instructions to appropriately reduce radiation exposures [9]. Outpatient ^{131}I treatment is absolutely contraindicated for patients who are unable to care for themselves, who live in nursing homes or who prefer not to be released after taking ^{131}I.

Justification for high-dose outpatient ^{131}I therapy

The fact of the matter is that internment after radioiodine therapy is almost never indicated for clinical reasons, and takes into account neither the interest of the patients and their lifestyle nor the health system status of each country. These practices usually increase the costs of therapy and are identified as a source of limitation for patient-care attendance, especially in developing countries where there is insufficient hospital space available for accommodating patients exposed to radiation. Studies have shown that a delay (of more than 180 days) in initial ^{131}I therapy after total thyroidectomy for well differentiated thyroid cancer may result in poor survival (risk of death is 4.22 times higher than those treated within 180 days). Furthermore, very little or no consideration for the patient's interests or needs was considered.

Allowing for treatments as outpatients not

only saves money but also influences decisions to choose ^{131}I treatment rather than surgical alternatives by patients (for toxic goitre ablation and treatment of low-bulk metastatic or recurrent thyroid carcinoma). More important is to consider the financial cost of the in-patient ^{131}I therapy in public or private sector healthcare facilities. For example, in Brazil, the cost of an ablative procedure, using 100-150 mCi of ^{131}I, is around $800 and $2500 in a public and a private healthcare provider system, respectively, involving 2 days of hospital internment in either case. In Pakistan, the cost of high-dose ^{131}I (<150 - >150 mCi) in public and private healthcare facilities is around $116-150 and $638-812 respectively. If the patient is released after high-dose ^{131}I treatment, the cost of therapy in and public and a private healthcare system may be reduced by 60% to 86%, respectively, which is a substantial saving indeed. In addition to making patient-care more efficient and economical, it also improves the quality of life for the patients and their families.

Opposition to new patient release criteria

In the US, NRC new recommendations (10 CFR 35.75), were criticized by some people due to their concern of radiation exposure from current practices [20]. In 2005, a petition was filed for partial revocation of patient release criteria rule 10 CFR 35.75 [21]. The *American Thyroid Association* submitted a response stating that radiation exposures within the homes did not exceed statutory limits in comparable studies performed in the United States [22], Canada [23] and Brazil [24]. Regarding the contamination from treated patients, no levels of contamination was found in home surveys in a study by Panzegrau *et al* [25]. Supporting the low potential for significant radiation exposure to the public, are the data of Venencia *et al* who treated 14 patients with 30-221 mCi of ^{131}I and found that the exposure did not approach 5.0 mSv until the treatment activity was greater than 187 mCi [26]. On the basis of these concrete evidences, the NRC upheld the rule (10 CFR 35.75) which remains in effect [9].

Current practice and need for paradigm shift in Pakistan

In Pakistan, Nuclear Regulatory Authority, PNRA (like the NRC in the US) is the statutory body, which ensures safe operation of nuclear facilities and the protection of radiation workers, general public and the environment from the harmful effects of radiation. This body formulates and implements effective regulations, builds a relationship of trust with the licensees and maintain transparency in its actions and decisions [27]. Regarding ^{131}I treatment, PNRA follows the "rule of 33 mCi" and recommends the licensee to isolate the patients given >33 mCi of ^{131}I for a period till residual radioactivity falls down to 30 mCi or dose rate is <7 mrem/h at 1 meter distance.

There are only few nuclear medicine centres (mainly in the big cities) in public and private sectors, which are licensed to treat patients with high doses of ^{131}I. However, due to limited isolation rooms available in these licensed facilities, long waiting lists (about 3-4 months) are not unusual with significantly high associated treatment costs (includes cost of ^{131}I and 2-3 days internment in isolation room). Furthermore, isolation has its own psychological and logistic impacts on families and patients too.

In the US, on the basis of tangible facts, the NRC amended its regulations in 1997, and again on the basis of evidence of no untoward effects of this practice, upheld it in 2009 too. We feel that the time has come for PNRA to also review its regulations in view of US NRC amendments and that it must allow the licensees to deliver high-dose ^{131}I therapy on an outpatient basis.

We presume that the PNRA feels that the social setup (small houses with relatively greater family members) and the literacy level of Pakistan, is different from the US and these facts aren't deniable. However, it is also a proven fact that a patient treated with <30

mCi ^{131}I for hyperthyroidism, may still deliver a significant radiation dose to the family members and the public if he/she does not follow the instructions given by Radiation Protection Officer (RPO) [4]. There is a large body of data revealing the fact that the risk from annual doses below 100 mSv is either too slight to be observed or nonexistent [13-17]. Also, various studies performed in different parts of the world have shown that the exposure from high-dose ^{131}I-treated patient to caregivers and family members is below the 5 mSv/year dose limit [26-30]. The PNRA must realize the fact that apart from the financial burden on the patients, a delay in ^{131}I treatment after total thyroidectomy results in a poor survival [22] considering that such delays are not uncommon in our set-up and hence demands a serious and sincere consideration on the part of PNRA.

On the basis of these tangible facts, the authors strongly feel that PNRA should revise its regulations so as to allow licensees to treat patients with higher doses of ^{131}I with the proviso that every patient must be given appropriate radiation safely instructions verbally and in writing as is being practiced in USA for the last 14 years with no untoward effects. Alternatively, PNRA may conditionally allow few nuclear medicine facilities with credentialed nuclear physicians and radiation protection officers to administer high-dose (>30 mCi) ^{131}I treatment on an outpatient basis to specified patients who can provide a proof of appropriate housing and their ability to understand and follow the given verbal and written instructions. We additionally recommend that the PNRA should provisionally collaborate with these potential therapy providers to collect data from the treated patients for validation of the amendments in its regulations.

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