"Boom-Boom" radioimmunotherapy of lymphomas: are two magic bullets better than one?

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Since its first human use, dated back to 1987 (1), radioimmunotherapy (RIT) of non-Hodgkin (NHL) lymphomas has undergone many vicissitudes, and we might be not too far from the truth by affirming that this is not the best time for it (2). As a matter of fact, the worldwide enthusiasm following the approval, at the beginning of this century, of the first two RIT compounds, ^{90}Y-ibritumomab-tiuxetan (Zevalin®) and ^{131}I-tositumomab (Bexxar®) for relapsed/refractory indolent NHL, was tempered by the success of new chemotherapy agents (3) and of the rituximab maintenance strategies (4). Moreover, in case of relapse after optimized rituximab-including treatments, RIT showed a reduced efficacy both in aggressive and indolent NHLs (5,6). In addition, the absence of randomized phase III studies comparing RIT head-to-head with other agents and the physicians' natural reluctance to refer patients to radionuclide treatments, have played in synergy against its use. At present, RIT is underused (*Figure 1*) and, in February 2014, this has led to the withdrawal of Bexxar® from the US market.

Yet, RIT is by far the most effective and least toxic single treatment for NHL, and it is largely preferred by patients over other therapeutic options (7-9); in fact, none of the available anti-cancer agents would be able to produce as high as 87% ORR (including 56% CR/Cru) or 95% ORR (including 75% CR/Cru) after a single infusion, as obtained with frontline Zevalin® or Bexxar®, respectively (7,8).

Interestingly, nuclear medicine has the intrinsic potential of allowing pre and post-therapeutic in-vivo biodistribution studies, which might inform the therapeutic infusion of RIT. By applying computational analysis on radioactivity distribution in organs or tumor lesions over time, internal dosimetry allows for obtaining dose calculations in these body compartments (*Figure 2*). Indeed, doses to organs and target lesions can vary intra and inter-patients because of the influence of all possible physical and biological variables in RIT, such as scheme of RIT fractionation, amount of antibody preloading, changes in size and biology etc. Unfortunately, such dosimetry studies are seldom accomplished in clinical practice, thought they might help to evaluate the effect of all these variables on RIT efficacy and toxicity, pursuing patient-specific treatment optimization.

Planar dosimety using a tracing amount of ^{131}I-labeled antibody is part of the standard protocol for Bexxar® infusion, where the therapeutic administered activity is planned on a single-patient basis in order to keep the resulting total-body dose (TBD) within a predetermined limit (i.e., <75 cGy or <65 cGy in patients with platelet counts ≥ or ≤150,000/mL, respectively). As a result, the range of administered therapeutic activity per single patient is wide, that is between 47 and 212 mCi (1.74–7.8 GBq), median 91 mCi (3.36 GBq) (10). Interestingly, a significantly longer duration of response was shown for patients receiving higher TBD (>65 cGy) if compared to patients receiving less than 55 cGy (11).

Conversely, the activity to be administered in RIT with the radiometal conjugate ^{90}Y-ibritumomab-tiuxetan takes into account patient weight and platelet blood count only, and no optimization based on pre-therapeutic dosimetry is considered.

The choice of avoiding dosimetry in case of Zevalin® has several reasons. First, the biodistribution of radio-metal conjugates is generally thought to be better
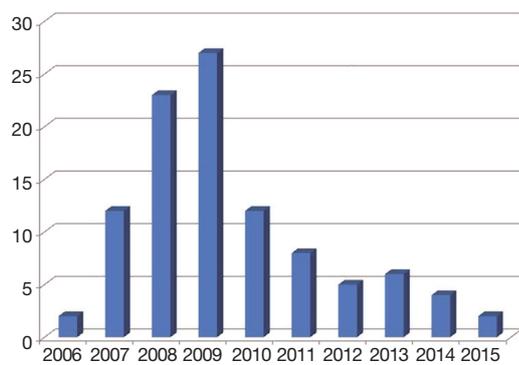
Figure 1 Distribution over time of a total of 101 radioimmunotherapy treatments with ^{90}Y-ibritumomab-tiuxetan (Zevalin®) performed at Sant'Andrea University Hospital of Rome, Italy, between July 2006 and October 2015.
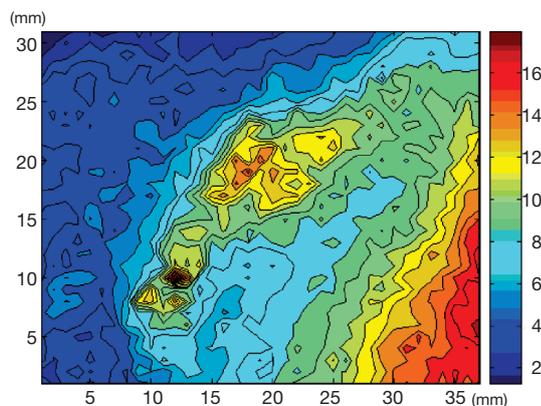
Figure 2 Isodose map at the pixel level of an axillary lymphoma lesion of follicular origin obtained by sequential planar γ-camera imaging after the injection of a tracing amount of ^{111}In-Zevalin. Dose values are reported in Gy.

predictable than that of radio-halogens. Second, dosimetry of ^{90}Y-ibritumomab is complicated by the technical impossibility of obtaining γ-camera images by means of the pure β-emitter ^{90}Y, which requires the labeling of ibritumomab with a γ-emitting surrogate, such as [111]In. Third, and probably of greater importance, the marketing of RIT compounds has preceded many recent technical and theoretical achievements of internal dosimetry which, when RIT was developed, was just not advanced enough to match clinical needs and expectations. In fact, radiobiological modeling has only recently been applied to radionuclide treatments and is continuously evolving as new questions arise from therapies implying different

physical and biological effects (12-14). In addition, only the breakthrough of hybrid SPECT/CT cameras has allowed accounting for errors and spatial heterogeneities in dose calculations, facilitating patient-specific voxel-based dosimetry and implementing radiobiological modeling (15). As such, standard planar dosimetry is no longer a good model for optimizing RIT efficacy, and three-dimensional, voxel-based dosimetry is warranted. Only recently three dimensional dosimetry and radiobiological modeling have been applied to RIT: a few reports have been published supporting a dose-response relationship for NHL nodal lesions treated with Bexxar® (16), while tumor voxel-based dosimetry of Zevalin® is still at its beginning (17,18).

In synthesis, much room does still exist for improvement of RIT efficacy and optimization of delivery and the feeling is that RIT is not only underprescribed but also underdosed.

An excellent effort toward dose optimization in RIT is represented by a recently published paper from a cooperative international research group reporting on the efficacy and toxicity of ^{90}Y-ibritumomab-tiuxetan delivered in two fractions as frontline therapy in patients with follicular lymphoma (FL) (19). From the 76 recruited, a total of 72 patients entered the final protocol; fifty-five patients (76%) received both infusions. Eight and four patients did not proceed with the second RIT infusion because of bone marrow toxicity (BM) and treating physician's discretion, respectively. Additionally, 4 patients developed mouse antibodies (HAMA) after the first cycle and one patient did not undergo the second infusion for underlining psychiatric disease. Most patients (78%) were stage III/IV; 44% patients had high-risk FLIPI. Patients with more that 20% BM infiltration were pretreated with four weekly infusions of rituximab 375 mg/m^2 and entered the study provided that <20% BM infiltration was achieved.

RIT infusions were administered 8 weeks apart, unless otherwise indicated by slow BM recovery. ^{90}Y-ibritumomab-tiuxetan was given at 11.1 MBq/Kg and injected activities were capped at 888 MBq (24 mCi). Such protocol showed an excellent 95.8% ORR including 69.4% CR/Cru, and a projected 3-year PFS of 58%. Interestingly, in contrast to previous observations, there was no significant difference in PFS between patients with tumor size < or >5 cm (65.4% *vs.* 50.2%, P=0.47). Hematological toxicity profile was acceptable: grade 4 thrombocytopenia and neutrophenia occurred in 6.9% and 8.3% of patients after the first infusion, increasing to 21.8% and 14.5% after the second infusion, respectively. After the second RIT, 8 (14.5%) patients received platelets and

the same number of patients received red cell transfusions. Two (2.8%) neutropenic sepses were observed in the entire cohort. It is worth reminding, however, that 8 patients (11% of the initial cohort) could not undergo the second RIT infusion because of prolonged BM suppression after the first treatment.

Dose fractionation has a strong theoretical rationale both in external beam radiation therapy (EBRT) and in RIT since, according to the classical linear-quadratic model, it makes possible to increase the total dose delivered to tumor by decreasing normal tissue toxicity. An additional advantage of dose fractionation in RIT would be the possibility to achieve more uniform dose distributions within tumors by progressively reducing tumor size and improving blood supply (20). However, the same radiobiological principles do not necessarily apply identically to both EBRT and RIT, as the latter involves heterogeneous, continuous and continuously decreasing low-dose-rate radiation, which effects on cell killing have yet to be fully understood (21). As a matter of fact, it is interesting to note that non-targeted effects, including apoptosis, mutations, cell transformation, release of stress signals, are probably prevalent in RIT as they occur after low dose or low dose-rate irradiation (21). These so called "bystander" effects might not be fitted by linear or linear-quadratic models, rather they might saturate after a certain dose threshold, questioning the superior efficacy of the dose-fractionation *vs.* standard, single treatment approach in RIT, which indeed has yet to be experimentally determined in patients (21). In addition, there are other non-radiation dependent immunological effects of RIT which might help to explain the excellent response of some tumor to very low radiation burden. For example, it has been suggested that the benefit of RIT would be higher in patients with preserved T cell immunity, which might complement the effect of radiation by eliciting a cell-mediated toxicity against the mouse monoclonal antibodies used in RIT (22).

Some responses to the radiobiological questions regarding efficacy of dose fractionation on tumor control in RIT might come from the study of Illidge *et al.* (19). A retrospective dosimetric analysis of 28 patients from this cohort revealed that organ absorbed doses were similar for both fractions and that an image-based, 3D method for BM dosimetry was predictive of hematological toxicity (23). Unfortunately, however, at the time of writing no data have yet been published on the results of tumor dosimetry in these patients.

Given its complexity and all the reasons we briefly outlined above, not surprisingly dosimetry was only retrospectively analyzed and not used to inform treatment schedule in this trial. Therefore, important radiobiologic and immunologic questions still need to be addressed. Nonetheless, the study of Illidge and colleagues is encouraging and could potentially pave the way for the conception and design of future trials aiming at a radiobiological optimization of RIT delivery. With particular regard to tumor dose-effect relationships, there might be a bulk of relevant information arising from combined dosimetric, clinical and laboratory data of this study, which would be otherwise lost if not fully analyzed and discussed. In other words, this study might have still a lot to say on the effects of RIT.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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