Myeloid neoplasms after chemotherapy and PRRT: myth and reality

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Abstract

Peptide receptor radionuclide therapy (PRRT) with ^{90}Y-octreotide or ^{177}Lu-octreotate is an effective treatment for inoperable or metastatic neuroendocrine tumors (NETs), particularly well-differentiated gastroenteropancreatic or bronchopulmonary NETs. PRRT is generally extremely well tolerated, with modest toxicity to target organs, kidney and bone marrow. Nevertheless, *a priori* concerns regarding long-term effects lead clinicians such as Brieau and coworkers, in this ERC issue, to ascribe to the combination of alkylating agents and PRRT the apparently high occurrence ($n=4$) of myeloproliferative events (therapy-related myeloid neoplasms (t-MNs)) in a small cohort of 20 progressive, advanced digestive NETs treated with PRRT after chemotherapy. Anecdotal reports of myelotoxic events should be placed in the correct perspective of larger series, where the reported incidence of these events is ~2%, with the aim of promoting a balanced awareness of the issue and unbiased and reasonable overall conclusions. For a comprehensive definition of the issue, we provide an evaluation of the occurrence of t-MN in patients treated with various myelotoxic treatments.

Key Words
- myeloid neoplasms
- alkylating chemotherapy
- PRRT
- neuroendocrine tumors

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Introduction

It is now widely accepted that peptide receptor radionuclide therapy (PRRT) is an effective treatment for inoperable or metastatic neuroendocrine tumors (NETs), particularly well-differentiated gastroenteropancreatic (GEP) or bronchopulmonary NETs. Twenty years of well-documented investigation in reputable institutions have yielded unequivocal evidence of efficacy with the commonly used radiopeptides, ^{90}Y-octreotide and ^{177}Lu-octreotate. The objective response rates range from 15 to 35% and the progression-free survival rates exceed 30 months. These results are recapitulated by the preliminary, as yet unpublished, randomized-controlled

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trial (NETTER-1) (Strosberg *et al*. 2015). The projected overall survival rates in the latter compare favorably with conventional therapies including somatostatin analogs, chemotherapy, and recently approved therapies including everolimus and sunitinib. Cumulative experience has led to widespread clinical acceptance of ^{177}Lu-octreotate as the radiopeptide of choice due to its favorable response rates and lower incidence of nephrotoxicity compared to ^{90}Y-octreotide.

PRRT is generally extremely well tolerated, with modest toxicity to target organs, kidney and bone marrow. Serious adverse events are scarce and mostly unpredictable, because their pathogenesis is poorly understood and, in some cases, apparently idiosyncratic (Frilling *et al*. 2014).

Main text

Toxicity associated with PRRT is categorized as acute, subacute or long term. Acute and subacute side effects are typically mild and self-limiting, comprising fatigue (common), nausea (25%, rarely vomiting), hair loss (maximum grade 1 60%), abdominal pain (10%) and occasionally hormonal crisis (1%) (Kwekkeboom & Krenning 2016). Nausea (controlled effectively by antiemetic therapies, e.g., granisetron) is related to concomitant administration of 'nephro-protective' amino acids (Bernard *et al*. 1997, Bodei *et al*. 2003). Other subacute side effects are radiation related (Kwekkeboom *et al*. 2005, van Essen *et al*. 2008, Kwekkeboom & Krenning 2016). Hematologic toxicity, the most common subacute side effect, is typically mild (WHO grades 1–2) and reverses within weeks of treatment cessation. More severe WHO grade 3 or 4 form (generally reversible within 2–3 months) occurs in <15% patients, irrespective of the radiopeptide utilized. However, in ~50% of these patients, it may persist (Kwekkeboom & Krenning 2016). The mean recovery time was 12 months in a series of 203 ^{177}Lu-octreotate-treated patients (Sabet *et al*. 2013). Neoplastic bone marrow involvement may increase the likelihood of myelotoxicity (Hubble *et al*. 2010). The majority of renal events are mild if the necessary precautions (such as nephroprotective amino acid coadministration and therapy adaptation to the clinical scenario) are undertaken (Bodei *et al*. 2009, Hofman & Hicks 2014). In a cumulative analysis of nine individual series, ~2500 patients/15 years, chronic and permanent effects to target organs were infrequent with ^{177}Lu-octreotate (Bodei *et al*. 2016). Loss of renal function grade 4 was 0.4%, reduced bone marrow reserve and, more infrequently, myelodysplastic syndrome (MDS) was 2–2.3% and leukemia (1.8%), respectively (Bodei *et al*. 2016).

The concepts of PRRT tolerability (and potential negative outcomes) differ considerably between nuclear medicine physicians and referring oncologists, endocrinologists, and gastroenterologists. The former group accentuates the rarity of PRRT-related toxicity, whereas the latter, who are concerned *a priori* about 'therapy-induced' adverse events, believe them to be directly induced by internal radiation therapies. The putative rationale is that PRRT is responsible for all cases of nephropathy and the induction of mutagenic bone marrow events. The latter position is exemplified by the communication by Brieau and coworkers published in this issue (Brieau *et al*. 2016). This letter describes an apparently high incidence of myeloproliferative events in the long-term follow-up (3.1 years) of a small cohort of 20 progressive, advanced digestive NETs treated with PRRT after chemotherapy. Four patients (20%) from a French oncology facility developed therapy-related myeloid neoplasms (t-MNs) 30–70 months after PRRT at the Erasmus Medical Center (EMC) Rotterdam. Compared to the rest of the cohort who also received PRRT, these 20 patients had more cycles of chemotherapy, more cycles of alkylating agents, experienced more frequent early high-grade hematotoxicity, and tended to more frequently have bone metastases. The authors infer that the very high occurrence of t-MN in this cohort was due to previous administration of alkylating agents and therefore that these agents should be avoided before PRRT, particularly in the management of low-grade NETs. Their conclusion was that the combination of alkylating agents and PRRT poses a high risk of MDS. It should be noted that the precise causal relationship between t-MN and PRRT remains elusive. Only a small percentage (~2%) of patients after ^{177}Lu-octreotate develop t-MN at the EMC (Kwekkeboom & Krenning 2016).

Although the association with collateral myelotoxic therapy, including chemotherapy or radiotherapy, has previously been suggested, mathematical analysis of a series of more than 800 patients has led to reconsideration of the association. (Bodei *et al*. 2015). Although any added information that amplifies the understanding of t-MN after myelotoxic therapies is valuable, we are of the opinion that the interpretation of the results reported in this useful communication appears alarmist and unduly skeptical. Our major concern is the focus on this subset of very advanced and heavily pretreated patients referred to another center to receive salvage PRRT. They neither represent a prospectively enrolled cohort treated with PRRT after chemotherapy nor do they accurately reflect the average patient. The letter

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regrettably depicts anecdotal events defined in a selected subset, thereby providing a degree of bias that has led to an unreasonable overall conclusion. As currently presented, this engenders an erroneous assertion to a physician unfamiliar with the complexities of the subject that PRRT, used in a multidisciplinary fashion together or after chemotherapy (a registered treatment), has a significant risk (20%) of causing MDS/AML. As noted, the pessimistic conclusions are reached in a small subset of over 700 patients treated with ^{177}Lu-octreotate at the EMC Rotterdam (Kwekkeboom *et al*. 2008). In this group, the estimated incidence of these events is ~2% (Kwekkeboom & Krenning 2016). Of additional concern is the argument that the occurrence of t-MN in the GEP–NET population treated with alkylating-based chemotherapy is only 1% (i.e., 1 of 95). This is misleading because patients are neither numerically matched nor matched for individual chemotherapy, years of follow-up, skeletal involvement, and so on. The presented analysis of a small subgroup of heavily pretreated and progressive patients referred to another center to receive salvage PRRT unfortunately reflects the current practice of utilizing PRRT in very advanced stages of disease. Such data cannot be utilized to signal a spurious negative alert regarding safety. In order to better define the issue and render it balanced, we have evaluated the occurrence of t-MN in patients treated with various myelotoxic treatments.

Myeloid neoplasms are considered either the consequence of mutational events induced by cytotoxic therapies or to arise via the selection of a myeloid clone with a mutator phenotype that has a markedly elevated risk for mutational events (Boehrer *et al*. 2009). MDS and AML secondary to chemo- or radiotherapy are a recognized category in the WHO 2008 classification (t-MN), as a nosologic group with a heterogeneous clinical outcome (Vardiman *et al*. 2009). The latency between diagnosis and therapy-related disease ranges from a few months to more than 10 years, depending on the cumulative dosage or dose intensity of therapy and exposure to specific agents (Godley & Larson 2008). The incidence of primary MDS is estimated at 3–20/100,000 and tends to increase with age (Rollison *et al*. 2008). No rigorous data that define the incidence of t-MN are available; estimates indicate a range of 10–15% of all MDSs. The overall risk of t-MDS is therefore low but not negligible. In the assessment of clinical trials of alkylating therapy, an incidence of 0.25–1% per year beginning 2 years after the initiation of therapy and decreasing 7 years after the completion has been reported (Churpek & Larson 2013).

The incidence of t-MN after chemotherapy trials exhibits large variations due to inherent selection biases, with the highest percentages reported with older forms of intensive treatments and smaller series (Churpek & Larson 2013, Candelaria & Duenas-Gonzalez 2015). Large series with extended follow-up are more reliable. In the SEER database (1975–2008), the occurrence of t-AML in more than 400,000 cancer patients treated with chemotherapy ± radiotherapy was 0.18%. This is 4 times higher than the normal population. Of note, radiochemotherapy combinations for solid cancers did not carry a significantly increased risk, compared with chemotherapy alone (Morton *et al*. 2013). Many conditions treated with alkylating agents have poor long-term survival, unlike that of low-grade NET, and therefore, estimates of the long-term impact of these agents on the development of t-MN may be underestimated.

t-MN secondary to radiation is more complex and is a multifactorial process that originates due to single- or double-strand breaks in the DNA, involving errors in repair mechanisms and genetic mutations, with loss of function or oncogene activation. A critical parameter is the different sensitivities of DNA to radiation during the cell cycle and intrinsic host repair mechanisms (Bourguignon *et al*. 2005). High-dose total body irradiation, as in atomic bomb survivors, Chernobyl nuclear disaster liquidators, or large-field conditioning radiotherapy before bone marrow transplantation, is known to be leukemogenic in a dose-dependent manner (Gluzman *et al*. 2015). However, the absolute rate of MDS is very low. A cohort study of Nagasaki A-bomb survivors identified only 198 cases out of 86,271 (0.2%) irradiated individuals followed for 40–60 years, with greatest risk among the young (Iwanaga *et al*. 2011). Although a potential increased risk of radiation therapy in association with chemotherapy has been reported (Sun *et al*. 2015), the relative contribution of chemotherapy to the incidence of t-MN is unclear. Follow-up of patients treated with chemotherapy for advanced Hodgkin lymphoma found t-MN in up to 2.7% (Engert *et al*. 2012). The mutagenic potential of lower doses of radiotherapy as used in modern radiation therapy planning, which greatly reduces the exposure of the bone marrow, is more controversial. This is especially relevant because many of the reported myeloid neoplasms share genetic features with *de novo* forms (Nardi *et al*. 2012, Cogle 2014, Zhang & Wang 2014). In such cases, the correlation with irradiation is debatable and is considered representative of epiphenomena that are either coincidental or reflect individual genetic susceptibilities (Zhang & Wang 2014).

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The same assertions may be made for radionuclide therapies, which are targeted therapies aimed at maximizing the target-to-normal tissue dose ratio, and exhibit a relatively limited total body distribution. One day after PRRT administration, radioactivity is typically <1% in the blood and <20% in the whole body, leading to cumulative red marrow and total body doses of ~1 and ~1.5 Gy, respectively (Cremonesi *et al.* 2010). t-MN after radionuclide therapies is considered uncommon and has only been sporadically reported with the various treatment modalities (radioiodine (RAI), ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) (Matthay *et al.* 2007)), radioimmunotherapies (^{131}I or ^{90}Y) (Leahy *et al.* 2006), and PRRT (^{111}In, ^{90}Y, and ^{177}Lu). As a consequence, studies are retrospective and statistical analyses include myeloproliferative events after radionuclide therapies generically encompassing the rubric of radiation therapy. Rigorous assessments are therefore not feasible.

Several studies combining the data of thyroid cancer patients of various age groups have shown that ^{131}I therapy may be associated with an increased risk for second primary malignancies (SPMs) (Rubino *et al.* 2003, Dottorini & Salvatori 2013). However, dose–response relationships between radioiodine therapy and the risk of SPM were found in only a few studies (Clement *et al.* 2015). Brown and coworkers reviewed 30,000 SEER patients and identified a significant increase in second malignancies among patients treated with ^{131}I (relative risk 1.16, $P<0.05$) (Brown *et al.* 2008), especially in younger patients. Another analysis of the SEER database ($n=27,775$ thyroid cancer patients surviving at least 5 years after diagnosis; 39% treated with RAI) reported a relative risk attributable to radioiodine of 1.12 (95% confidence interval (CI) 1.01–1.25) (Berrington de Gonzalez *et al.* 2011). A meta-analysis of RAI literature ($n=16,502$) revealed a 2.5-fold risk increase of leukemia (Grudeva-Popova *et al.* 2007). A separate systematic review of European and North America cohorts identified a 10–20% increase in secondary malignancies and that each GBq of ^{131}I increased the risk of a second solid cancer by an average of 3.5% and of leukemia by 39% (Sawka *et al.* 2004). Whether this increase resulted from aggressive treatment or an underlying predisposition to cancer remains unclear because cause–effect relationships are difficult to establish. It is possible that these figures also reflect the longer life expectancy of thyroid cancer. In the Dusseldorf MDS Registry, t-MN following radioiodine therapy was 5% (8 of 173), with a median latency of 79 months. The karyotype was abnormal in 68%, with aberrations noted most frequently in chromosomes 7, 5, 8, and 3 and a poor survival similar to those of patients with t-MN following other cytotoxic treatments (Schroeder *et al.* 2012*a*). In a separate cohort from Marseille ($n=10$), 60% of the AL karyotypes had unfavorable characteristics. This suggests that four patients had *de novo* features, with an as yet undefined relationship to cytotoxic events (Gilabert & Prebet 2012).

The non-Hodgkin lymphoma group of neoplasia is at considerable risk of developing secondary bone marrow neoplasms due to extensive myelotoxic treatments. The incidence of t-MDS was 2.5% (19 patients of 746 NHL treated with ^{90}Y-ibritumomab tiuxetan), occurring at a median interval of 5.6 years from the primary chemotherapy and 1.9 years after radioimmunotherapy. The underlying cytogenetic aberrations, the time from the exposure, and the expected number of t-MNs were consistent with the previous exposure to chemotherapy, and the expected incidence was not increased by the radioimmunotherapy. The authors suggested that cytogenetic testing in heavily pretreated patients might identify those more likely to develop t-MN (Czuczman *et al.* 2007).

In comparison to other therapies, PRRT constitutes a relatively recent intervention. t-MN events have been sporadically reported after ^{111}In-pentetreotide, ^{90}Y-octreotide and ^{177}Lu-octreotate (Kwekkeboom *et al.* 2010). A recent analysis of the largest cohort available ($n=807$ treated with ^{90}Y- and/or ^{177}Lu-peptides) identified an incidence of 2.34% for MDS and 1.8% for leukemia (75% evolved from MDS) (Bodei *et al.* 2015). The median latency from exposure was 4.4 years (Bodei *et al.* 2015). These data as well as those from the work of Brieau and coworkers suggest that the development of marrow neoplasms most likely is a consequence of previous treatments, such as chemotherapy. The percentage of cases with anomalous karyotypes after PRRT is, unfortunately, not known.

Given the demonstrable issue of secondary myeloid neoplasms, the need to predict or accurately assess the risk of such events is crucial. A clear dose–effect relationship, evident and linear with the dose for irradiation such as nuclear blasts (Gluzman *et al.* 2015), is not apparent in radionuclide therapies such as PRRT. In the latter, the doses delivered to the bone marrow are generally low (mean 0.02–0.07 Gy/GBq), resulting in a mean dose, for typical administrations of 7.4 GBq, of 0.15–0.5 Gy. This is well below the threshold of 3.7 Gy for a single administration, as reported for radioiodine (Garkavij *et al.* 2010, Lassmann *et al.* 2010, Sandstrom *et al.* 2013). Despite the theoretical appeal correlating individual bone marrow

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doses with adverse effects, dosimetry has failed to provide a reliable instrument to predict myeloproliferative events in PRRT. A key issue is the difficulty in accurate bone marrow modeling (Cremonesi *et al*. 2010). In a cohort of 34 dosimetry-assessed patients, Bodei and coworkers, failed to demonstrate a clear correlation between dose and occurrence of t-MN. Furthermore, neither the amount of administered radioactivity nor the type of radionuclide employed had a significant impact on the occurrence of marrow neoplasms. This, together with the observation that only 29% of MDS and 22% of leukemia could be mathematically modeled by clinical data, suggests that intrinsic, genetically determined factors may have a critical role in the pathobiology of t-MNs (Bodei *et al*. 2015). This is substantiated by observations in radioiodine therapy for thyroid diseases where no difference could be established in the incidence of myeloid neoplasia between high activities used for cancer and low activities for benign diseases (Schroeder *et al*. 2012*b*). Such observations support the hypothesis of a preexisting biological (genomic) susceptibility to a radiation-induced effect.

In a *post hoc* analysis of t-MN etiopathology, it remains scientifically challenging to identify particular perpetrators. It is therefore important to resist the simplistic temptation to explain all events on 'known knowledge'. Although it is generally accepted as a *fait accompli* that a myelotoxic event is linked to myelotoxic therapies (cytotoxics or radiation), other explanations require consideration. It remains essential to rigorously identify and define stochastic events, susceptibility to mutagenic events, and myeloid neoplasia predisposition, irrespective of exposure (Churpek & Larson 2013, Bueso-Ramos *et al*. 2015). It is noteworthy that many authors have proposed a role of individual genetic predisposition (Kitamura *et al*. 2014). The likelihood of an intrinsic molecular genomic basis is further supported by the increased incidence of myeloid neoplasia in Fanconi anemia, Li–Fraumeni syndrome, neurofibromatosis type 1, Down syndrome, as well as in circumstances characterized by genetic polymorphisms of enzymes involved in the metabolism of cytotoxic agents (e.g., glutathione *S*-transferase) (Liew & Owen 2011, Churpek & Larson 2013).

We agree that, in the absence of an accurate, personalized assessment of the individual risk of developing radiation associated disease, the use of radionuclide therapies in patients heavily pretreated with alkylating agents remains a cause for concern. The possibility of developing a t-MN can never be ignored. However, anecdotal reports of myelotoxic events should be placed in the correct perspective of larger series, with the aim of promoting a balanced awareness of the issue rather than an emotional response that diminishes the utility and efficacy of the therapy. An incidence of an adverse event of 2–3% is worthy of clinical evaluation using a thoughtful risk–benefit ratio assessment (Strosberg *et al*. 2015) rather than succumbing to any unduly pessimistic assessment.

To move toward a more modern and personalized assessment of risk, in future evaluation of therapy, individual radiosensitivity will need to be assessed by specific biomarkers, such as chromosomal screening of bone marrow of patients potentially at risk, γ-H2AX assays (Denoyer *et al*. 2015), and genetic testing. An unmet need is the availability of pre- or intratherapeutic assessment of circulating transcriptional markers to predetermine or delineate impending neoplastic marrow events. The latter require identification and development for application to PRRT and other radiopharmaceutical therapies. The necessity for national registries as well as multidisciplinary assessments with mathematical integration of clinical, dosimetric, biomarker and genetic information is clearly needed. This will enable the development of objective risk assessment nomograms and facilitate risk–benefit quantification based upon impartial analysis of results obtained in long-term follow-up of large cohorts of comparable patients. Nevertheless, based on the data presented in the letter as well as our own experience with PRRT, we believe that the treatment of patients with low-grade tumors with alkylating chemotherapy should be avoided, and preference should be given to PRRT due to its the relatively high response rate, prolonged associated survival and low toxicity. More importantly, patients should avoid treatments associated with long-term toxicity unless there are uncontrolled symptoms or objective evidence of disease progression that, if unchecked, would lead to reduction in quality and duration of life.

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