VIA MEDICA

Techniki napromieniania

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2017, tom 2, nr 5, 389–395

ISSN 2543–5248
www.biuletyn.nowotwory.edu.pl

Bone marrow sparing RT in era of immunotherapy

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Recent advances in the field of immunotherapy have changed the perception of cancer treatment to complex model with host immunity in the spotlight. Potential synergy of immunotherapy drugs [aiming cytotoxic T cell antigen 4 (CTLA-4) or programmed cell death-1/ligand (PD-1/PD-L1)] and radiotherapy (RT) have established basis for ongoing clinical trials testing combined treatment. It was shown that complete blood cell counts (CBC) parameters may correlate with cancer survival, toxicity and outcomes of treatment. Therefore, reduction of hematologic toxicity of cancer treatment may gain in significance. Modern dose delivery techniques compromise dose reduction in critical organs (like bone marrow — BM) with adequate irradiation of target volumes. In addition, usage of modern imaging like positron emission tomography (PET), magnetic resonance imaging (MRI) allows to divide the volume of BM to active and inactive one.

In this review, we discuss the synergy of RT and immunity and techniques of Bone Marrow Sparing RT (BMS-RT).

Biuletyn PTO NOWOTWORY 2017; 2, 5: 389–395

Key words: radiotherapy, intensity-modulated radiotherapy, bone marrow, red bone marrow, yellow bone marrow, immunotherapy, lymphopenia, neutropenia, thrombocytopenia, anaemia

Introduction

The twentieth century was a period of great discoveries in oncology. The first major successes were associated with local treatment of solid tumors. The development of surgical techniques and discovery of ionising radiation were the main factors that enabled successful treatment of patients with locally advanced stages of cancer. Extensive local treatment has been replaced with more precise one with adjuvant treatment, a good example can be the treatment of breast cancer [1, 2]. In the recent years, alongside surgery, chemotherapy and radiotherapy (RT), immunotherapy has become recognizable as the fourth pillar of oncology with possible synergy with RT [2, 3]. The idea of significant role of immunity in cancer is not new. Injections of malignant cells to prevent cancer were described as early as in 1777, than they were clinically investigated in sarcomas with cure rate of 10% in year 1891 [4]. Immunotherapy has a history of ups and some spectacular downs, such as disappointing results of vaccines against cancer cells [4]. In recent years conventional perception of tumor "detached from microenvironment" have changed to more complex model where radiosenstivity of cells is affected by host immunocompetence [5]. Anti-tumor specific host immunity can be enhanced by cancer cell death, induced by radiation [2]. Studies concerning combined RT with checkpoint blockade immunotherapy have cast new light on the subject [2]. Moreover, efforts are being made to explain how anticancer treatment can harm patient immunology system [6, 7]. In view of the fact that immunotherapy relies on host's own immunity, the prevention of

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Artykuł w wersji pierwotnej:
Kuncman Ł, Pietrzykowska-Kuncman M, Danielska J, Łuniewska-Bury J, Fijuth J. Bone marrow sparing RT in era of immunotherapy. *NOWOTWORY J Oncol* 2017; 67: 301–307.

Należy cytować wersję pierwotną.

hematologic toxicity (HT) due to cancer treatment seems to be important. One of the investigated approaches to reduce RT related HT is bone marrow sparing RT (BMS-RT). Highly conformal RT techniques allow to reduce radiation dose in bone marrow (BM) without deterioration of dose coverage of target structures [8]. Most of active bone marrow in adults is localized in pelvis [8]. Highly conformal RT techniques are not routinely used for all cancers in this region, because of scarcity of clinical trials and concerns about target movement [9]. In this review, we discuss advantages of different kinds of BMS-RT. Recent discoveries in immunotherapy are also briefly reviewed.

RT and immunity

Host immune status is believed to influence the natural history of cancer [10, 11]. The immunoediting hypothesis along with possible stages of cancer cells existence (elimination, equilibrium, dormancy, escape) show role of host own immunity in cancer survival [12, 13]. There is a substantial body of evidence that late recurrences and long term survival depend on immune mediated equilibrium [13]. Lymphocytes are involved at various steps of host response to cancer, and may modulate response to treatment [14, 15]. Lymphopenia and decreased ratio of lymphocytes to neutrocytes or platelets might be prognostic factor in survival for various cancer types [16–19]. Moreover pretreatment lymphopenia was proposed to predict survival and early death after chemotherapy for breast cancer, lymphomas and sarcomas [20, 21]. d'Engremont et al. found pre- and post--operative lymphopenia to be an independent prognostic factor for survival in patients with pancreatic cancer [22]. Similarly, severe lymphopenia was shown to predict poor survival in patients after chemoradiotherapy (CRT) for cervical cancer [23]. Baseline complete blood count cells (CBC) predict occurrence of HT during whole pelvis RT (WPRT) for prostate cancer [24].

The balance between tumor induced immuno-suppression and immuno-enhancing pathways is crucial in cancer survival [14]. Moreover, duality of effect (pro and anticancerous) is observed in cancer therapy [25]. In unfavorable situation eradication of tumor cells may be nullified by host immunity reactiveness, repopulation and malignant clones selection [25]. Radiotherapy or CRT was generally considered to be immunosuppressive because of observed reduction in blood cell counts [2, 26]. Ionizing radiation causes DNA damage thus rapidly dividing cells such as neoplasm cells, leucocytes and lymphocytes with its precursors are prone to RT [3, 26]. Drop in CD8+ and CD4+ lymphocytes with increased expression of programmed cell death-1 (PD-1) receptors were observed during CRT of cervical cancer [27]. Authors concluded that CRT suppresses immune system and thus combination of RT and immunotherapy could be difficult [27]. 2-D planning RT and imperfect imaging techniques required large treatment field. This in turn causes unintended irradiation of healthy tissues including bone marrow, blood pool, local lymphatic system [2, 3]. With the development of modern precise treatment the immune-compromising effect of RT can be significantly reduced [2, 3].

The synergy between RT and immunity must be considered in broad context. Lee et al. demonstrated that tumor control was different in immunocompetent and nude mice (without T CD8+ and some B lymphocytes) by ablative RT [15]. In this melanoma model regression depended on T CD8+ lymphocytes [15]. The body of preclinical data and casuistic reports suggest that RT has the potential to enhance response to immunotherapy and vice versa immunotherapy can modify tumor microenvironment and radiosensitivity of cancer cells [28]. Cytotoxic T cell antigen 4 (CTLA-4) and PD-1/PD-L1 checkpoints are significant molecular brakes which prevent T cells from hyperactivity and in patients with cancer can suppress natural host defense against cancer [10, 29]. In addition to promising results of immunotherapy as single method, the results of animal based studies show the synergy between RT and inhibitors of CTLA-4 and PD-1/PD-L1 checkpoints [30, 31]. Anti PD-1/ /PD-L1 checkpoints drugs enable T cells to influence tumor microenvironment and to decrease the number of suppressive cells [14]. Improved survival or local control was demonstrated for combined radiotherapy and anty PD-1/ /PD-L1 treatment for gliomas, melanomas, breast carcinomas animal models [32, 33]. Preclinical studies provided the evidences for more than 20 ongoing trials testing the effect of combined immuno-radiotherapy treatment [34].

The abscopal effect (AE) (regression of cancer lesions outside of RT filed), although described in 1950's, was postulated to be immune mediated five decades later by Demaria et al. [35, 36]. This phenomenon, rarely observed in clinical routine when RT is administrated alone, has recently become more commonly reported when RT is combined with immunotherapy [14]. Postow et al. and then others reported AE in melanoma and non-small cell lung cancer patients treated with Ipilimumab and RT [37–41]. Golden et al. conducted trial reporting occurrence of AE in 26,8% of patients with oligometastatic breast, lung and thymic cancer treated with granulocyte-macrophage colony-stimulating factor and palliative regiment of RT [42]. AE was observed in 52% of patients treated with palliative RT after progression on Ipilimumab [38]. Authors concluded that AE may correlate with prolonged overall survival [38].

Both immunosuppressive and immunenhancing mechanism of RT and immunity have been comprehensively reviewed by Weichselbaum et al. [14]. Equilibrium of these effects is believed to have huge impact on cancer treatment success [14]. Various groups of mechanisms how irradiation influences cancer cells and microenvironment have been

described in details [14]. The aforementioned preliminary data suggest that radiotherapy and immunity can influence cancer natural history. Taking into account interaction between RT and host immunity (especially lymphocyte status), therapeutic strategies to preserve patient natural immunity during cancer treatment may gain in significance.

Bone marrow sparing RT

Radiotherapy has undergone remarkable transformation in the field of treatment precision [43]. Progress from 2D radiotherapy and imaging to image guided, dynamic 3D irradiation techniques and molecular imaging, enables us to spare organs at risk (OAR) and escalate radiation dose inside target volumes [44, 45]. BMS-RT advantages should be the most appreciated in large treatment fields encompassing axial skeleton (skull, spine, sternum, clavicles, scapulas, pelvis) where the vast majority of red (active) bone marrow is localized in adults [46]. Approximately half (40–50%) of bone marrow is localized in pelvic region [47, 48]. Majority of available clinical data describes the application of intensity modulated radiation therapy (IMRT) for BMS-RT for prostate, cervical, rectum, anal cancers [47, 49–58]. In macroscopic cervical and rectum cancer dynamic irradiation techniques are still not first-line treatment options due to concerns over internal organ motion [8, 9, 59]. They should be applied with caution and accompanied with image guidance when significant dosimetry advantage in OAR is achieved [9, 48, 59]. National Comprehensive Cancer Network (NCCN) guidelines indicate that IMRT should only be administrated for unique clinical situation like reirradiation or inside clinical trials [9]. Limited data regarding BMS-RT are available for esophageal and gastric cancer [60, 61]. Two main approaches for BMS-RT are: 1) dose reduction in total bone marrow (BMtot)-delineated as entire bone volume near planning target volume and 2) division of bone marrow on basis of functional imaging to red (active) bone marrow (BMact) and yellow (inactive) bone marrow (BMinact).

Total bone marrow sparing RT in treatment area

In the era of RT used as a single method of treatment, HT was not clinically significant sequalae, attention was focused on gastrointestinal or urinary toxicity [48, 62]. In the recent two decades when CRT for cervical, rectum, anal, gastric cancer have become widespread, HT is one of the most common side effects of combined treatment [63]. IMRT was found to reduce HT/dose to BM, even without dose constrains for BMtot in IMRT in CRT for cervical, anal and rectal cancer [53, 62, 64, 65]. IMRT was reported to reduce low (not confirmed by all authors) and high doses to BM volume [53, 65–68]. IMRT due to higher amount of leakage dose may affect distant sites of BM [69]. Differences in dose distribution in BM were observed mostly in iliac BM [62]. With dose restrictions for BMtot, in IMRT planning, reduction in doses delivered to BMtot can be more significant [67, 70–72]. In recent analysis Mell et al. has suggested that positron emission tomography (PET) guided IMRT can further decrease the incidence of HT [8]. There is no consensus, which dose constrains are crucial to reduce HT, moreover available data are based on small groups studies, what limit its application to daily clinic. Many investigators suggest that low and medium doses ≤ V20 may be most relevant for HT in CRT of pelvic region [47, 49–51]. Mell et al. found that pelvic BM-V10, BM-V20 was associated with ≥ grade 2 leukopenia (BM-V10 additionally with neutropenia) in CRT for cervical cancer [47]. In another paper Mell et al. showed that Pelvic BM-V5-V20 was correlated with decreased white blood cell count (WBC) and absolute neutrophils count (ANC) nadirs in CRT for anal cancer [49]. Albuquerque et al. suggested that only BM-V20 was correlated with grade 2 HT in CRT for cervical cancer patients [50]. Similarly, Rose et al. concluded that BM-V10 ≥ 95% and BM-V20 > 76% dose constrains predict grade ≥ 3 leukopenia in CRT for cervical cancer [51]. Contrary to those findings, Klopp et al. in analysis of HT in RTOG 0418 trial indicated that BM-V40 was associated with occurrence of grade 2 HT in CRT for cervical cancer [52]. In CRT for rectal cancer Yang et al. showed that patients with coxal (bilateral ilium, ischium and pubic) BM-V45 and sacral BM-V45 experienced lower WBC and ANC nadirs [53]. In another paper, Wan et al. indicated that lumbosacral BM--V40 predicted grade ≤ 2 HT in CRT for rectal cancer [54]. In the study including 100 women, Chang et al. noted that IMRT was superior to 3-D RT in medium and high doses (BM-V20, BM-V30, BM-V40) and mean BM dose [55]. Those parameters were most significant for HT in CRT for cervical cancer [55]. Noteworthy RapidArc plans presented higher mean BM dose, BM-V10 and BM-V40 than IMRT [55]. In the biggest study including 121 chemonaïve prostate cancer patients, Sini et al. demonstrated that BM-V40 predicted acute grade 3 and late grade 2 lymphopenia [24]. Analysis by Zhu et al. supported thesis of significant role of multiple doses-volume parameters in BM [56]. BM-V20, V30 and V40 were found to predict HT (V10 border significance) [56]. The researchers estimated that every 1 Gy of BM mean dose decreased ln (ANC) by 9.6/μL per week [56]. Franco et al. confirmed importance of BM-V20 for WBC nadir and lower pelvis BM-V40 for grade 3 acute HT [58]. Multiplicity of dose volume parameters connected with HT may lead to conclusion that bone marrow function is affected by both low and high doses. Moreover mean bone marrow dose may be significant for HT in CRT of cervical and anal cancer) [56, 57]. Bazan et al. suggest that mean BM dose 22,5Gy and 25Gy predicted 5 and 10% risk of HT [57]. In view of above papers, BM acts as parallel organ and whole spectrum of doses may be significant [57].

Many other risk factors such as body mass index, gender, smoking, complete blood count (CBC) at baseline, cancer

clinical stage were evaluated as predictors for HT, with no consistent conclusions in different studies. Baseline CBC parameters seem to be independent predictors for HT [24, 49]. Although association of gender, body mass index (BMI) with HT was shown, it might be, in fact, result of different shape/volume of pelvis [49, 73]. It may influence dose distribution in pelvic BM [73].

Subregions bone marrow sparing RT

Large pelvic bone marrow volume and shape surrounding pelvic organs make it technically challenging to reduce dose in the whole pelvic BM. Identifying the most clinically relevant regions of BM may be a solution. It was shown that IMRT allows to reduce dose to active bone marrow effectively without compromising the coverage of target and organs at risk (OAR) [74]. Mell et al. divided pelvic bone marrow to lower pelvis (LP) (comprising ischium, pubic and proximal femora) lumbosacral spine (LSS) and ilium (IL) [47]. They found that LSS-V20, LP-V10 and LP-V20 correlated with grade 2 HT for CRT of cervical cancer [47]. LSS-V5 to 20 was associated with ANC and WBC nadirs in anal cancer patients [49]. Yang et al. (as described above) showed that specific regions of BM were associated with acute HT [53]. Sini et al. proposed a model for 1-year lymphopenia with iliac BM dose metrics [24]. The subvolumes of BM based on bone anatomy still remain large. Further attempts were made to reduce volume of delineated BM to only BMact. BMact cannot be distinguished from BMinact on basis of computer tomography [75]. Promising results were shown in studies concerning functional imaging such as PET, magnetic resonance imaging (MRI) and spectroscopy (SPECT) [8, 61, 74, 76–79]. Restriction of delineated volume of BM, when entered as constraint for IMRT plan, result in significant reduction of dose in BMact, irrespective of technique used for delineation of BMact (MRI, SPECT, PET) [80–82].

MRI delineation of active bone marrow bases on different chemical and cellular composition of red BMact and yellow BMinact [83]. BMact made of fat-40%, water-40% and protein-20% exhibits on T1-weighted images as region of signal intensity equal or lower than that of muscles [80, 83]. BMinact consists of fat-80%, water-15% and protein-5% and is hiperintense on T1-weighted sequence of MRI [80, 83]. V5-BMact identified on MRI was correlated with decreased WBC, ANC, platelets count (PLT) nadirs in CRT for rectal cancer [76]. Multivariate analysis of data of CRT in gastric cancer revealed correlation between dose volume metrics of BMact and nadirs of CBC (increased V20-BMact resulted in decreased WBC and ANC nadirs) [61]. As MRI is routinely administered before radiotherapy of most cancers in pelvis, it is a valuable tool to delineate BMact [9, 59, 84]. The two main disadvantages of delineation based on T1 MRI are that it is rather subjective (not based on any parametrical values) and it is time consuming due to the fact that it is performed manually [61, 76]. Recently published analysis on semi-automated BMact segmentation on basis of Dixon sequence of MRI may be the solution, but must be evaluated in more details [75]. Fat composition changes were observed after radiotherapy which were correlated with CBC parameters [85].

Another approach to distinguish BMact and BMinact is application of (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET), (18)F-fluorothymidine positron emission tomography (FLT-PET) and spectroscopy [86, 87]. Regions of BM with standard uptake value (SUV) greater than patient's mean were proposed to represent BMact and can be used as constrain for IMRT plan [8, 77, 88]. Wyss et al. compared feasibility of FDG-PET and FLT-PET and concluded that although FLT-PET had minor individual variation, both methods findings were consistent [78]. Rose et al. found the correlation between mean dose in BMact delineated on basis of FDG-PET before CRT for cervical cancer and log (WBC) nadirs, log (ANC) nadirs, PLT nadirs [77]. BMact--V10, BMact-V20, BMact-V30 were associated with decreased log (WBC), however no correlations were shown for BMinact [77]. Elicin et al. observed reduction of volume of FDG-PET based BMact after CRT for cervical cancer [79]. It was correlated with V30-BMact and reduction in WBC [79]. Various dose volume parameters of BMtot and BMact correlated with late HT in Elicin's study [79]. McGuire et al. observed FLT-PET BMact volume during and after CRT for cervical cancer [82]. Authors indicated that even the dose of 4Gy reduced SUV of BMact by 50% and was correlated with the time of occurrence of acute HT [82]. Doses greater than 35Gy caused chronic suppression of BM (measured as reduction of SUV) [82]. Recently published first multicenter trial by Mell et al. has tried to compare PET BMact sparing IMRT and whole pelvic BMtot sparing IMRT [8]. Although authors have observed reduced HT in PET BMact sparing group, they have reported that in this group, dose volume parameters for the whole pelvic BMtot were significantly lower as compared to "without PET" BMtot sparing group [8]. They have admitted that the mechanism of reduced toxicity in PET BMact sparing group is not fully explained and can indeed be the consequence of dose reduction in pelvic BMtot rather than BMact [8].

The indirect proof of relevance of PET based delineation of BM may be a decreased SUV in BM regions after irradiation in FDG-PET imaging [79, 89, 90]. BM suppression (measured as reduction of SUV) correlated with different CBC values [79, 89]. Further improvement of BM sparing RT can be achieved with the implementation of proton beams [91]. Dinges et al. created alternative proton beam plans for IMRT FLT-PET BM sparing RT and showed dosimetric advantage in the whole dose range; at least: 23% (for V5-BMact), 37% (for V10-BMact), 41% (for V20-BMact) and 39% (for V40-BMact) [91].

Conclusion

In view of the recent studies, hosts own immunity plays a key role in cancer survival and efficiency of cancer treatment. Although no mature data is available, in view of published studies, effort to reduce immunosuppressive effect of cancer treatment, may gain in significance. BMS--RT is a promising approach which leads to the reduction of HT. Greater number of studies confirm the correlation between dose-volume parameters of BMtot and HT than the correlation of dose-volume parameters and BMact and HT. However, it is technically more effective to reduce a dose to smaller volume such as BMact. Dose-volume parameters of BM considered as clinically relevant differ in studies, some have borderline significance. Further studies on large cohorts and metaanalysis of above papers are necessary.

Conflict of interest: none declared

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Received: 14 May 2017
Accepted: 16 June 2017

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