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APSTRAKT 1S 2024; 5(1): 1–2 ABSTRACT 1E

Aferezno prikupljanje ćelija iz periferne krvi i lečenje ćelijama – posredovanom hemobioterapijom imunski-posredovanih i nekih malignih poremećaja primenom DC i car T-ćelija

Apheresis Collection of Cells from Peripheral Blood and Treatment with Cell-mediated Chemotherapy of Immune-mediated and Some Malignant Disorders Using DC and CAR T-cells

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Apstrakt

Pored nadoknade deficitarnih sastojaka krvi suportivnom primenom hemoprodukata, hemoterapija podrazumeva korišćenje procedura afereze radi prikupljanja plazme ili krvnih ćelija (aferezna donacija), i uklanjanje ili zamenu abnormalnih ili prekomernog broja krvnih kostituenata, uz postizanje imunomodulacijskog ili hemomodulacijskog efekta (terapijska afereza – TAph). Osnovni cilj TAph je da smanji „opterećenje bolesnika" patogenim agensima (supstratom), koji su odgovorni za razvoj bolesti, na nivoe koji će omogućiti kliničko poboljšanje.

Hemoterapija, takođe, obuhvata prikupljanje matičnih ćelija (MĆ) – za transplantaciju i za upotrebu u regenerativnoj medicini – kao i prikupljanje, ex vivo manipulaciju i (re)infuziju imunokompetentnih ćelija radi postizanja ćelijama-posredovanih pozitivnih efekata. Uopšteno, imunoterapija uključuje upotrebu monoklonskih antitela, vakcina, ćelijama-posredovanih terapijskih modaliteta radi identifikacije i eliminacije malignih ćelija.

Vakcine sa dendritičnim ćelijama (DC) veoma dobro ilustruju aktivnu, ćelijama-posredovanu imunoterapiju. Osnovni cilj je da aktivišu efektorske T ćelije i da indukuju uništavanje malignih ćelija. Terapiju karcinoma zasnovanu na primeni DC ili strategiji vakcinisanja moguće je okarakterisati povoljnim terapijskim potencijalom i bezbednošću – uz nedostatak toksičnosti, u poređenju sa drugim terapijama maligniteta (visoko-dozna hemioterapija). U našem Odeljenju za aferezu i hemoterapiju prikupljanje MNC je izvedeno korišćenjem aparata Spectra-Optia – kao inicijalna faza DC-posredovanog tretmana bolesnika sa karcinomom prostate (PCa; n = 35). Ćelije su prikupljene iz krvi bolesnika u fiziološkoj ravnoteži hematopoeze. Periferne (antekubitalne) vene su korišćene kao vaskularni pristup, a ponekad je primenjen centralni venski kateter (n = 3) upotrebom vene subklavije ili jugularnih vena. Bolesnicima je data antikoagulacija sa ACD-A (koncentracija citrata = 2,2%). Volumen procesirane krvi tokom pojedinačnih procedura afereza bio je 9684,0 ± 2016

Abstract

In addition to compensating for deficient blood components with the supportive use of chemo products, chemotherapy involves the use of apheresis procedures to collect plasma or blood cells (apheresis donation) and the removal or replacement of abnormal or excessive blood components, while achieving an immunomodulating or chemo modulating effect (therapeutic apheresis). The main goal of therapeutic apheresis is to reduce the "load of the patient" with pathogenic agents (substrate), responsible for the development of the disease, to levels that will enable clinical improvement.

Chemotherapy also includes the collection of stem cells – for transplantation and for use in regenerative medicine – as well as the collection, ex vivo manipulation and (re)infusion of immunocompetent cells to achieve cell-mediated positive effects. In general, immunotherapy involves the use of monoclonal antibodies, vaccines, cell-mediated therapeutic modalities to identify and eliminate malignant cells.

Dendritic cell (DC) vaccines very well exemplify active, cell-mediated immunotherapy. The main goal is to activate effector T cells and to destroying malignant cells. Cancer therapy based on DC application or vaccination strategy can be characterized by favorable therapeutic potential and safety – with a lack of toxicity compared to other malignancy therapies (high-dose chemotherapy). In our Department of Apheresis and Chemotherapy, MNC collection was performed using the SpectraOptia system - as the initial phase of DC-mediated treatment of patients with prostate cancer (PCa; n = 35).

The cells were gathered from the blood of patients in physiological balance of hematopoiesis. Peripheral (antecubital) veins were used as vascular access, and a central venous catheter was sometimes used (n = 3) using the subclavian or jugular veins. Patients were given anticoagulation with ACD-A (citrate concentration = 2.2%). The volume of processed blood during individual apheresis procedures was 9684.0±2016 mL, and the total volume of ACD-A used was 691.3±98.2 mL on average. The mean volume of the collected

mL, a ukupna zapremina korišćenog ACD-A je u proseku iznosila 691,3 ± 98,2 mL. Srednji volumen suspenzije prikupljenih ćelija bio je 179,9 ± 29,6 mL. U ovoj grupi bolesnika neželjeni događaji (hipokalcemija izazvana toksičnošću citrata) nisu konstatovani.

Terapija „himernog-antigen-receptora" T (CAR-T) ćelijama počinje prikupljanjem autolognih MNC (limfocita) iz periferne krvi (PB) bolesnika leukaferezom (MNC-afereza), bez primene rHuG-CSF. Nakon prikupljanja, autologni limfociti i/ili monociti bolesnika podvrgnuti su transdukciji gena. Naime, proces ex vivo manipulacije predstavlja transdukciju gena korišćenjem lentivirusnih ili retrovirusnih vektora. U fazi „pre-reinfuzije", kod bolesnika je primenjen citoreduktivni tretman radi smanjenja broja limfocita u cirkulaciji. Manipulisani i reinfundirani autologni limfociti usmereni su protiv tumorskih ćelija bolesnika.

Na osnovu podataka iz literature, kao i sopstvenih rezultata, moguće je zaključiti da uprkos razvoju ekspertize i dobijenim povoljnim rezultatima primenom CAR-T ćelija u hematoonkologiji, solidni tumori i dalje predstavljaju veliki terapijski izazov. Međutim, nesumnjivo je da ćelijama-posredovana terapija treba da bude sastavni deo lečenja karcinoma, uključujući i metastatski karcinom prostate rezistentnog na kastraciju (mCRPCa).

Prema tome, u proteklim decenijama ćelijama-posredovana imunoterapija postala je efikasan inovativni terapeutski „alat" za brojne uznapredovale karcinome, uključujući donekle i mCRPCa. Za definitivnu potvrdu početnih kliničkih rezultata potrebna su buduće randomizovane studije, sa većim brojem ispitivanih bolesnika.

Ključne reči: afereza, leukafereza, ćelijama-posredovana hemobioterapija, dendritske ćelije, CAR-T ćelije, karcinomi

cell suspension was 179.9±29.6 ml. In this group of patients, no adverse events (hypocalcemia caused by citrate toxicity) were noted.

Therapy with "chimeric-antigen-receptor" T (CAR-T) cells begins with the collection of autologous MNC (lymphocytes) from the patient's peripheral blood (PB) by leukapheresis (MNC-apheresis), without the use of rHuG-CSF. After collection, the patient's autologous lymphocytes and/or monocytes are subjected to gene transduction. Namely, the process of ex vivo manipulation represents gene transduction using lentiviral or retroviral vectors. In the "pre-reinfusion" phase, cytoreductive treatment was applied to the patient in order to reduce the number of lymphocytes in the circulation. Manipulated and reinfused autologous lymphocytes are directed against the patient's tumor cells.

Based on data from the literature, as well as our own results, it is possible to conclude that despite the development of expertise and the favorable results obtained with the use of CAR-T cells in hemato-oncology, solid tumors still represent a great therapeutic challenge. However, there is no doubt that cell-mediated therapy should be an integral part of cancer treatment, including metastatic castration-resistant prostate cancer (mCRPCa).

On that account, in the past decades, cell-mediated immunotherapy has become an effective innovative therapeutic "tool" for numerous advanced cancers, including to some extent mCRPCa. For a definitive confirmation of the initial clinical results, future randomized studies with a larger number of examined patients are needed.

Key words: apheresis, leukapheresis, cell-mediated chemotherapy, dendritic cells, CAR-T cells, cancer