Acta Biomed 2024; Vol. 95, N. 5: e2024102 DOI: 10.23750/abm.v95i5.15559

A pilot study of activity of pembrolizumab and low dose chemotherapy in relapsed/refractory T-cell lymphoma: Jordanian experience

Salah Abbasi[1], Haytham Dwaik[2], Layla Abbasi[2], Huda Al Hourani[3]

[1]Hematology and Oncology, Internal Medicine Department, Al-Khalidi Medical Center, Amman, Jordan; [2]Internal Medicine Department, School of Medicine, The University of Jordan, Amman, Jordan; [3]Department of Clinical Nutrition and Dietetics, Faculty of Applied Medical Sciences, The Hashemite University, Zarqa, Jordan

Abstract. *Background and aim*: Peripheral T-cell lymphomas (PTCLs) are associated with poor prognosis and limited treatment options in the relapsed/refractory (R/R) setting. Programmed cell death-1 and ligand-1 (PD-1 and PD-L1) are frequently expressed in T-cell Lymphoma. It provides a rationale for using immune checkpoint inhibitors (ICIs) to manage PTCLs. Many studies in solid tumors showed higher efficacy of ICIs when used in combination with chemotherapy. *Methods:* A study of 11 patients with R/R PTCLs was conducted retrospectively. They were treated at two Jordanian hospitals with Pembrolizumab, Vincristine, and Cyclophosphamide every three weeks. *Results:* The overall response rate (ORR) was 63%, with three complete responses (C.R.) and four partial responses (P.R.). The median progression-free survival (PFS) was 4.0 months (95% CI: 1.7 to 11.4), and the median overall survival (O.S.) was 17.0 months (95% CI: 0.7 to 33.2). *Conclusions:* Pembrolizumab and low-dose chemotherapy demonstrated promising activity in R/R PTCL, with high response rates. Furthermore, extensive studies are needed to define the role of such an approach. (www.actabiomedica.it)

Key words: peripheral T-cell lymphoma, pembrolizumab, immunotherapy, chemotherapy

Introduction

Peripheral T-cell lymphomas (PTCLs) comprise a group of lymphoproliferative disorders originating from mature T/natural killer (N.K.) cells and accounting for 10-25% of non-Hodgkin lymphomas (NHLs) (1). There are 27 subtypes of PTCL according to the World Health Organization 2016 classification of lymphoid neoplasm (2). Of these, extranodal N.K./T-cell lymphoma, nasal-type (ENKTL-NT), which is closely associated with Epstein-Barr virus (EBV) infection, is the most common in East Asian countries (3). Other common subtypes of PTCL include PTCL, non-specific (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic lymphoma kinase (ALK)+/– anaplastic large cell lymphoma (ALCL) (2,4). PTCLs are highly heterogeneous, aggressive, and generally incurable except for ALK+ ALCL and early-stage ENKTL. PTCLs are also associated with poor prognosis and are often resistant to cytotoxic chemotherapeutic drugs. The therapeutic options are limited, especially for relapsed or refractory R/R PTCL, and the median PFS and O.S. are usually less than six months (5). New, effective treatments are urgently required.

Studies have shown that the tumor microenvironment (TME) in PTCL is profoundly immunosuppressive (6,7). Although the TME in lymphoid malignancies is made of a mixture of various inflammatory cells, it remains ineffective against the malignant

cells. Program death ligands (PD-L) 1 and 2, expressed on antigen-presenting cells, activated T cells, and even on tumor cells, (8) interact with program death receptor 1 (PD-1) on T cells, leading to an inhibitory signal with subsequent T cell function exhaustion and energy, providing lymphoma cells a mechanism to evade immune surveillance (8). Furthermore, interactions between PD-1 and its ligands are even more unusual in PTCL because both the receptor and ligands can be expressed on the malignant T-cell (9). While it is reasonable to target the PD-1/PD-L axis in the TME to improve outcomes in PTCL, there is a potential for malignant T cells to be activated, which could be associated with inferior outcomes.

The administration of ICIs in hematological tumors, primarily classic Hodgkin lymphoma (cHL), has developed fast in recent years (10). Classical H.L. proves to be a promising target for anti-PD-1 therapy because PD-L1 is overexpressed by Reed-Sternberg cells (11), and PD-1 blockade Nivolumab has been tested in many clinical trials and obtained favorable results (12,13). It was also evaluated in a cohort of patients with relapsed or refractory lymphoid malignancies, including 29 with B-cell non-Hodgkin lymphoma (B-NHL), 2 with primary mediastinal large B cell lymphoma (PMBCL), and 23 with T-cell non-Hodgkin lymphoma (T-NHL). Four (36%) patients with Diffuse Large B Cell Lymphoma (DLBCL), four (40%) with F.L., two (15%) with mycosis fungoides (M.F.), and two (40%) with PTCL responded to the therapy, among whom one patient (9%) with DBLCL and one (10%) with follicular lymphoma (F.L.) achieved complete remission (C.R.) (14,15). NHLs generally do not share cHL's vulnerability to PD-1 inhibitors, and most NHLs appear to be minimally sensitive to PD-1 blockade (16).

A phase II study of Nivolumab enrolled 12 patients with R/R PTCL—including six with AITL, three with PTCL-NOS, and one with ALK–ALCL—half of whom had received autologous stem cell transplantation (ASCT). The overall response rate (ORR) was 33%, including two C.R.s and two partial remission (P.R.s), with median duration of response (DOR), PFS, and O.S. of 3.6, 1.9, and 7.9 months, respectively (17). Pembrolizumab was evaluated in a phase II multicenter study that enrolled eight patients with R/R PTCL. Treatment with this agent was stopped early after a preplanned interim analysis for futility (18). Another study included seven patients with R/R ENKTL with a median number of treatment lines two or more before enrollment. All patients had used dexamethasone-methotrexate-ifosfamide-asparaginase and etoposide (SMILE) or SMILE-like regimens, and two had relapsed after receiving allogeneic hematopoietic stem-cell transplantation (allo-HSCT). The ORR was 100% after a median of 7 weeks of treatment, with a median follow-up of 6 months. Five patients achieved sustained C.R., including two that achieved C.R. in all parameters. Patients with high PD-L1 expression had a better prognosis (19). Another study also recruited seven patients with R/R ENKTL and achieved a median ORR of 57% after four courses, including two instances of C.R. and two of P.R., with response duration, PFS, and O.S. of 4.1, 4.8, and 5.0 months, respectively. No direct relationship was observed between PD-L1 expression and treatment response (20).

Low-dose chemotherapy was added to improve the activity of pembrolizumab in R/R PTCL.

Study Design

Patients and treatment

Eleven Patients with R/R PTCL diagnosis (PTCL-NOS, AITL, ALK- ALCL, systemic M.F.) who were treated with Pembrolizumab were retrospectively evaluated. Pembrolizumab was given at 200mg every three weeks in all patients. All patients received pembrolizumab in combination with low-dose chemotherapy (Vincristine 1.4 mg/m^2 and Cyclophosphamide 750 mg/m^2) every three weeks as well, up to six cycles only, then continued pembrolizumab alone until disease progression, death, or toxicity.

All patients were fully informed about the nature and possible toxicities of the treatment protocol and gave informed consent.

Response assessment and monitoring

Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT) was used to assess response according to the Revised Lugano Response Criteria for Malignant Lymphoma (21,22). Because this study was retrospective, the schedule of PET/CT varied, but early assessment after 3 to 4 cycles was adopted in all cases and every 3 to 4 cycles after that.

Results

Patients

Eleven patients were included in the study analysis (Table 1). Three females and nine males. The median age was 45 years; range 29-82 years. 46% (5/11) had PTCL-NOS, 36% (4/11) had ALK- ALCL, 9% (1/11) had M.F., and 9% (1/11) had AITL.

The median number of prior lines of therapies was 3, with a range of 2-4 therapies. Three patients had received a prior autologous bone marrow transplant (27%).

Responses and survival

Seven patients had a response to pembrolizumab (ORR 63%), including four PR (36%) seen in patients with PTCL-NOS (two patients), M.F. (one patient), and ALK- ALCL (one patient); three C.R. (27%) were observed in PTCL-NOS (two patients) and ALK- ALCL (one patient).

The median PFS for the eleven patients was 4.0 months (95% CI: 1.7 to 11.4), as shown in Figure 1. The median O.S. was 17.0 months (95% CI: 0.7 to 33.2) for the whole group (Figure 2). The median O.S. for different pathologies was 5.0, 6.0, 54.0, and 17.0 months (for ALK- ALCL, AITL, M.F., and PTCL-NOS respectively). Three patients were alive at the last follow-up (two patients with PTCL-NOS and one with ALK-ALCL), as shown in Figure 2.

Table 1. Characteristics of the eleven patients included in the study.

Age (yrs)	Gender	Diagnosis	Previous treatments	Refractory to the previous line	Previous BMT
82	F	ALK- ALCL	CVP/Bendamustine/Radiation	No	No
57	M	M.F. / Sezary syndrome	PUVA/CHOP/high dose methotrexate	Yes	No
29	M	PTCL-NOS	CHOEP/DHAP/Brentuximab	No	Autologous
41	F	PTCL-NOS	CHOEP/Brentuximab/ESHAP	No	Autologous
29	M	PTCL-NOS	Bendamustine and Brentuximab	No	Autologous
35	F	ALK- ALCL	CHOEP/GDP/SMILE/Brentuximab and CHP	Yes	No
37	M	AITL	CHOEP/DHAP	Yes	No
31	M	PTCL-NOS	CHOEP/GDP/SMILE	Yes	No
72	M	ALK- ALCL	CHOP/RT and CVP/Brentuximab and Bendamustine	Yes	No
56	M	ALK- ALCL	CHOP/RT/Brentuximab	Yes	No
30	M	PTCL-NOS	CHOEP/ Brentuximab and Bendamustine	No	No

Abbreviations: ALK- ALCL, ALK-negative anaplastic large cell lymphoma; M.F., mycosis fungoides; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; cyclophosphamide-vincristine and prednisone (CVP), cyclophosphamide-doxorubicin -vincristine and prednisolone (CHOP), cyclophosphamide-doxorubicin-etoposide-vincristine and prednisone (CHOEP), dexamethasone-cisplatin and high dose cytarabine; (DHAP), gemcitabine-dexamethasone and cisplatin (GDP), dexamethasone-methotrexate-ifosfamide-asparaginase and etoposide (SMILE), cyclophosphamide-adriamycin and prednisolone (CHP), bone marrow transplant (BMT).

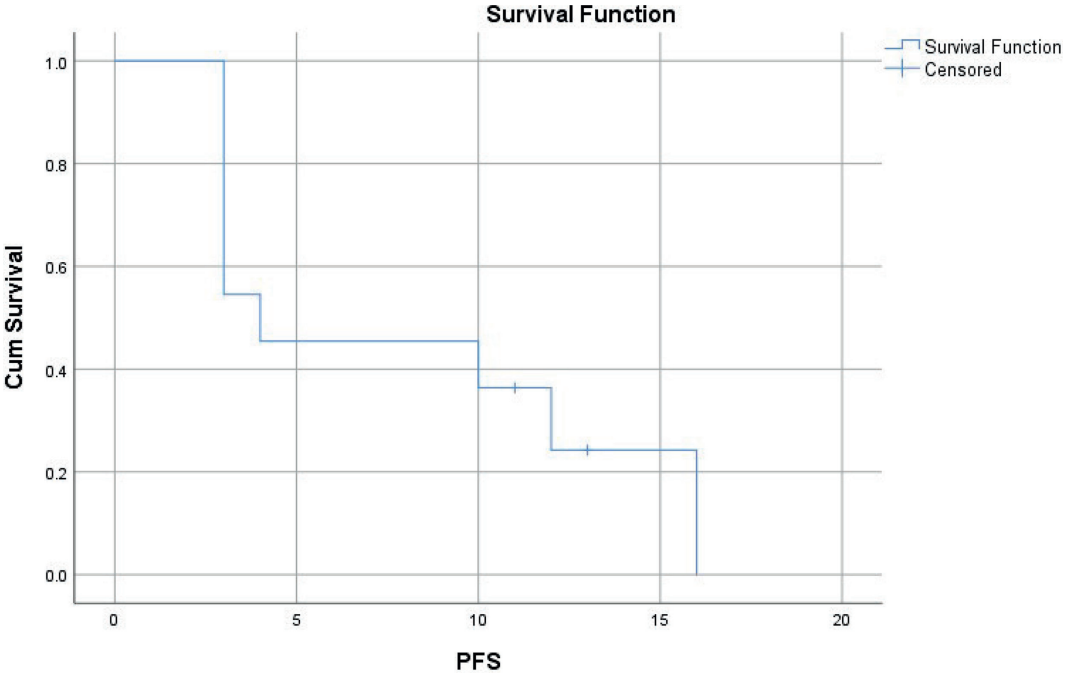

Figure 1. Progression-free survival curve for the whole group. Kaplan-Meier analysis was used to estimate the time of events.

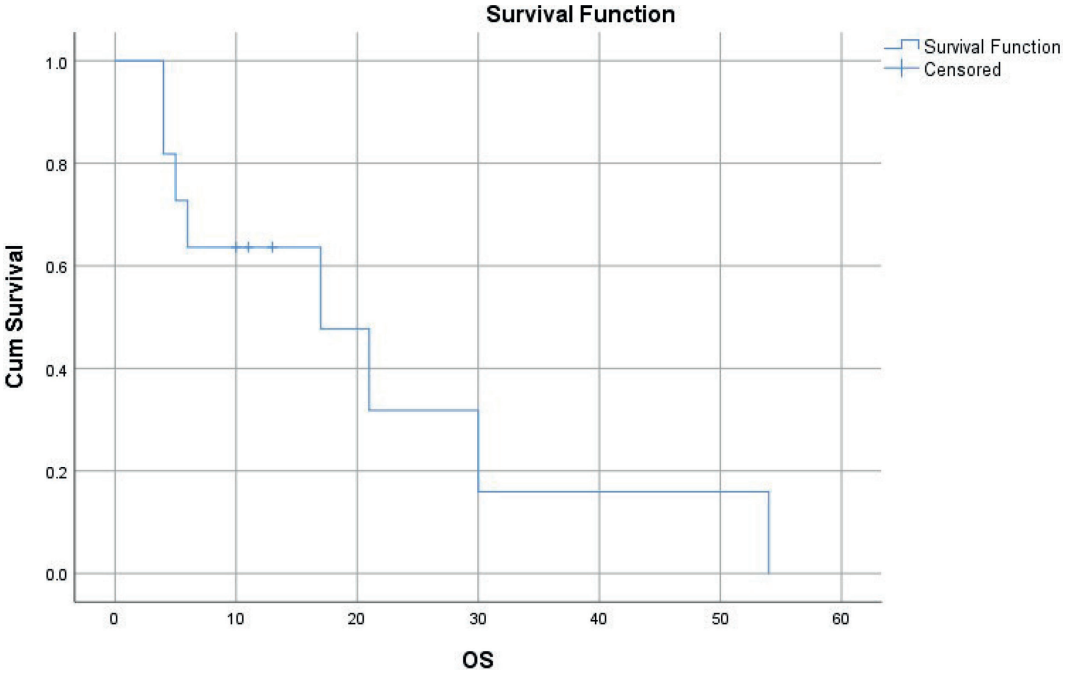

Figure 2. Overall survival curve of the whole group. Kaplan-Meier analysis was used to estimate the time of the event.

Discussion

Standard therapies in the relapsed setting in PTCL have been associated with modest responses at best, and many patients do not benefit from these agents. The rate of response seen with therapies used to manage R/R PTCL, such as histone deacetylase inhibitors romidepsin (23), belinostat (24), and the antimetabolite pralatrexate (25), is in the range of 25%–30% and is often short-lived.

ICIs showed modest activity in such patients. One study shows that PD-1 blockade with nivolumab in patients with RR PTCL has similar activity to currently used therapies with an ORR of 33% (26). The results of this study were consistent with a similar study using pembrolizumab, another PD-1 checkpoint blocker (18).

The use of nivolumab alone was associated with some cases of hyperprogression, which led to the halt of the study (26).

We used pembrolizumab in combination with low-dose chemotherapy that would act synergistically with checkpoint blockers and could help prevent hyperprogression. The results were promising, with higher response rates than previously published studies, including three patients with C.R. (27%). Also, the O.S. was dramatically higher, reaching a median of 17 months for the whole population, including a median O.S. of 17 months for PTCL-NOS and 54 months for M.F. The O.S. was not significantly different for other pathologies like ALK- ALCL and AITL. We did not see any cases of hyperprogression or unusual side effects. High response rates can help in bridging patients to allogeneic bone marrow transplants.

Conclusion

The combination of pembrolizumab and low-dose chemotherapy demonstrated promising activity in R/R PTCL, with high response rates. More broadly, research is also needed to define the role of ICIs in combination with other compounds active in PTCL, especially in histologies like PTLC-NOS or M.F.

Funding: None

Ethics Committee: The ethics committee and IRB approved the protocol at Al Khalidi Hospital (protocol # 427/8/23, date 15/08/2023). All patients were fully informed about the nature and possible toxicities of the treatment protocol and gave informed consent.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: L.A. and H.D. designed and collected the data; S.A. designed the research, interpreted the data, and wrote the manuscript; H.Al. analyzed the data and managed submission. All authors approved the final version of the manuscript.

References

1. Vose J, Armitage J, Weisenburger D, International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-30. doi:10.1200/JCO.2008.16.4558.
2. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-90. doi:10.1182/blood-2016-01-643569.
3. Yoon SE, Song Y, Kim SJ, et al. Comprehensive analysis of peripheral T-cell and natural killer/T-cell lymphoma in Asian patients: A multinational, multicenter, prospective registry study in Asia. Lancet Reg Health West Pac. 2021;10:100126. doi:10.1016/j.lanwpc.2021.100126.
4. Liu W, Ji X, Song Y, et al. Improving survival of 3760 patients with lymphoma: Experience of an academic center over two decades. Cancer Med. 2020;9(11):3765-74. doi:10.1002/cam4.3037.
5. Mak V, Hamm J, Chhanabhai M, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. J Clin Oncol. 2013;31(16):1970-6. doi:10.1200/JCO.2012.44.7524.
6. Bennani NN, Ansell SM. Tumor Microenvironment in T-Cell Lymphomas. Cancer Treat Res. 2019;176:69-82. doi:10.1007/978-3-319-99716-2_3.
7. Wilcox RA, Wada DA, Ziesmer SC, et al. Monocytes promote tumor cell survival in T-cell lymphoproliferative disorders and are impaired in their ability to differentiate into mature dendritic cells. Blood. 2009;114(14):2936-44. doi:10.1182/blood-2009-05-220111.

8. Tsushima F, Yao S, Shin T, et al. Interaction between B7-H1 and PD-1 determines initiation and reversal of T-cell anergy. Blood. 2007;110(1):180-5. doi:10.1182/blood-2006-11-060087.
9. Wilcox RA, Feldman AL, Wada DA, et al. B7-H1 (PD-L1, CD274) suppresses host immunity in T-cell lymphoproliferative disorders. Blood. 2009;114(10):2149-58. doi:10.1182/blood-2009-04-216671.
10. Strome SE, Dong H, Tamura H, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res. 2003;63(19):6501-5.
11. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood. 2010;116(17):3268-77. doi:10.1182/blood-2010-05-282780.
12. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372(4):311-9. doi:10.1056/NEJMoa1411087.
13. Ansell SM. Nivolumab in the Treatment of Hodgkin Lymphoma. Clin Cancer Res. 2017;23(7):1623-6. doi:10.1158/1078-0432.CCR-16-1387.
14. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. J Clin Oncol. 2016;34(23):2698-704. doi:10.1200/JCO.2015.65.9789.
15. Xia Y, Jeffrey Medeiros L, Young KH. Signaling pathway and dysregulation of PD1 and its ligands in lymphoid malignancies. Biochim Biophys Acta. 2016;1865(1):58-71. doi:10.1016/j.bbcan.2015.09.002.
16. Merryman RW, Armand P, Wright KT, Rodig SJ. Checkpoint blockade in Hodgkin and non-Hodgkin lymphoma. Blood Adv. 2017;1(26):2643-54. doi:10.1182/bloodadvances.2017012534.
17. Bennani NN, Kim HJ, Pederson LD, et al. Nivolumab in patients with relapsed or refractory peripheral T-cell lymphoma: modest activity and cases of hyperprogression. J Immunother Cancer. 2022 Jun;10(6):e004984. doi:10.1136/jitc-2022-004984.
18. Barta SK, Zain J, MacFarlane AWt, et al. Phase II Study of the PD-1 Inhibitor Pembrolizumab for the Treatment of Relapsed or Refractory Mature T-cell Lymphoma. Clin Lymphoma Myeloma Leuk. 2019;19(6):356-64 e3. doi:10.1016/j.clml.2019.03.022.
19. Kwong YL, Chan TSY, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory N.K./T-cell lymphoma failing l-asparaginase. Blood. 2017;129(17):2437-42. doi:10.1182/blood-2016-12-756841.
20. Li X, Cheng Y, Zhang M, et al. Activity of pembrolizumab in relapsed/refractory N.K./T-cell lymphoma. J Hematol Oncol. 2018;11(1):15. doi:10.1186/s13045-018-0559-7.
21. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86. doi:10.1200/JCO.2006.09.2403.
22. Fournier L, Ammari S, Thiam R, Cuenod CA. Imaging criteria for assessing tumour response: RECIST, mRECIST, Cheson. Diagn Interv Imaging. 2014;95(7-8):689-703. doi:10.1016/j.diii.2014.05.002.
23. Coiffier B, Pro B, Prince HM, et al. Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol. 2012;30(6):631-6. doi:10.1200/JCO.2011.37.4223.
24. O'Connor OA, Horwitz S, Masszi T, et al. Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study. J Clin Oncol. 2015;33(23):2492-9. doi:10.1200/JCO.2014.59.2782.
25. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol. 2011;29(9):1182-9. doi:10.1200/JCO.2010.29.9024.
26. Bennani NN, Kim HJ, Pederson LD, et al. Nivolumab in patients with relapsed or refractory peripheral T-cell lymphoma: modest activity and cases of hyperprogression. J Immunother Cancer. 2022;10(6). doi:10.1136/jitc-2022-004984.

Correspondence:
Received: 26 December 2023
Accepted: 16 April 2024
Huda M. Al Hourani, Prof
Department of Clinical Nutrition and Dietetics, Faculty of Applied Medical Sciences
The Hashemite University, P.O. Box 330127, Zarqa 13133, Jordan
E-mail: hhourani@hu.edu.jo
ORCID: 0000-0001-7017-6499