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Long-term outcomes of reduced-dose bleomycin in electrochemotherapy for basal cell carcinoma in elderly patients

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Electrochemotherapy (ECT) is a minimally invasive treatment option for basal cell carcinoma (BCC), which is particularly advantageous in the elderly population. This study evaluated the long-term effects of treating BCC in older patients using ECT with a reduced dose of bleomycin (10,000 IU/m^2) and compared the results to patients who received the standard dose of bleomycin (15,000 IU/m^2). The retrospective analysis included 116 patients aged over 65 years with 257 histologically confirmed BCCs. Tumors were treated with either the standard dose (n = 82) or the reduced dose (n = 175) of bleomycin. The results showed that the recurrence rate was comparable between the groups, particularly in the first year after treatment. The reduced-dose group exhibited a greater recurrence rate after the first year, which may be attributed to a weaker local immune response due to the de-escalated dose of bleomycin. Nonetheless, administering a standard bleomycin dosage as a salvage treatment in the event of recurrence proved highly effective. These findings suggest that ECT with a reduced bleomycin dose is a viable option for treating BCC in elderly patients, particularly those with shorter life expectancy.

Keywords Bleomycin, De-escalation, Head and neck, Electrochemotherapy, Nonmelanoma skin cancer

Basal cell carcinoma (BCC) represents the most prevalent form of cutaneous malignancy, accounting for more than 3 million cases worldwide each year. Its incidence continues to rise globally, particularly in populations with high exposure to ultraviolet radiation. Although BCCs are slow-growing and rarely metastasize, their potential for local invasion necessitates prompt and effective treatment to prevent significant tissue destruction[1,2]. Treatment modalities for BCC include surgical excision, Mohs micrographic surgery, cryotherapy, radiotherapy, and topical pharmacotherapy, among others[3,4]. Electrochemotherapy (ECT), which combines electroporation with the administration of cytostatic agents such as bleomycin, has emerged as a promising therapeutic option for treating BCC[5]. This technique enhances the cytotoxic efficacy of bleomycin by increasing cell membrane permeability, facilitating hydrophilic drug uptake, and promoting tumor cell apoptosis. ECT can damage the vasculature of the tumor via vasoconstriction and through its late cytotoxic effect on the endothelium, leading to the entrapment of bleomycin.[6] It also induces a local immune reaction that contributes to overall antitumor effectiveness of ECT[7].

The integration of ECT into the therapeutic arsenal for BCC offers a minimally invasive alternative with a favorable side effect profile, particularly for patients with surgically challenging lesions, multiple lesions, or those for whom traditional surgical approaches are contraindicated. The favorable outcomes obtained in ECT of BCCs include objective response rates nearing 100% following a single session of ECT[8]. The standard operating procedure (SOP) recommends intravenously administering a bleomycin dose of 15,000 IU/m^2 of body surface area[9]. Conversely, pharmacokinetic and clinical studies suggest the feasibility of using a reduced dose of bleomycin, particularly in the elderly population due to altered elimination and distribution of bleomycin[10,11]. This could be the result of different body compositions with different ratios of water to fat and structural changes

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within the renal tissue[12]. The latter involves a reduction in the number of functional glomeruli, primarily due to nephrosclerosis, which is reflected in reduced creatine clearance[13].

When considering BCC treatment in elderly patients, it is crucial to tailor the approach on the basis of overall patient health status, existing comorbidities, and personal preferences[14]. The high prevalence of chronic conditions in this demographic group necessitates careful dose adjustments, particularly regarding the reduction in bleomycin dosage to maintain therapeutic efficacy while minimizing potential side effects[15]. This strategy not only promotes a more rapid healing process with favorable cosmetic outcomes but also enhances overall quality of life[16]. There is a lack of comprehensive studies that employ a reduced dose of bleomycin with ECT in the treatment of skin tumors, particularly BCC. Research groups investigating the efficacy of a lower bleomycin dose have focused on a wide range of tumors or skin neoplasms, often involving relatively small patient cohorts[11,17]. Additionally, these studies have assessed the effects of reduced doses over a short period, commonly up to two months. Given the slow-growing nature of BCC and its tendency toward late recurrence, extended monitoring periods are warranted[18]. This study sought to elucidate the long-term (up to 8.8 years) response to a reduced bleomycin dosage in ECT for elderly patients with BCC and compare the outcomes to those of patients treated with the standard bleomycin dose.

Materials and methods

Study protocol with follow-up

This retrospective study was conducted at the Department of Otorhinolaryngology and Cervicofacial Surgery, University Medical Centre Ljubljana and Institute of Oncology Ljubljana on patients with BCC initially treated with ECT between June 2014 and July 2023. The protocol was approved by the National Medical Ethics Committee of the Republic of Slovenia (Permit No. 182/02/14, 0120-132/2015-2). The procedures were conducted in accordance with national guidelines and per the Helsinki Declaration, with a written informed consent obtained from each included patient.

The study included patients with biopsy- or cytology-confirmed BCC within the head and neck region who underwent ECT with intravenous bleomycin. All included patients were older than 65 years. The indication for ECT for each individual was determined by a multidisciplinary head and neck tumor board. Detailed selection process for ECT with bleomycin was based on the inclusion and exclusion criteria, which have been documented elsewhere[11,16] and were consistent with SOP for ECT[9].

The patients were classified into two groups according to the received dose. The control group consisted of patients who received a standard dose of intravenously administered bleomycin (15,000 IU/m^2) with ECT. The standard dose has been chosen according to the ESOPE and SOP guidelines as the lowest effective dose that results in the least side effects[9,19]. The second group consisted of patients who underwent ECT with a reduced bleomycin dose (10,000 IU/m^2), which was based on a study on bleomycin pharmacokinetics in elderly oncologic patients[10]. Elderly patients who were treated until the publication of the previous pharmacokinetics study received a standard dose of bleomycin[11], whereas patients aged over 65 years subsequently received a reduced dose of bleomycin.

The demographic characteristics of the patients, such as sex/age, largest tumor diameter, tumor number, previous treatment strategies, tumor response, and salvage treatments, were recorded and then compared. The response to treatment was clinically evaluated according to the RECIST guidelines, version 1.1[20], in ambulatory settings. These evaluations were generally made two, four, six, twelve, eighteen, and twenty-four months after the treatment and annually thereafter. The exact follow-up time differed between the patients and was dependent on tumor location and size, wound healing, previous treatment strategies, and the patient's general health status. In the event of disease recurrence, an individualized treatment plan was made for each patient, opting for surgical excision, radiotherapy, or salvage ECT with bleomycin at the standard dose.

Electrochemotherapy procedure

The procedure was performed according to the SOP guidelines under local/general anesthesia or sedation. The bleomycin obtained from Medac (Wedel, Germany) was administered as a single bolus of 2 min, followed by electric pulses 8 min after the end of administration. The patients in the control group received a dose of 15,000 IU/m^2, whereas those in the reduced group received a dose of 10,000 IU/m^2. Needle row electrodes were employed for ECT, and the pulses were generated using a generator of electrical pulses (Cliniporator, Igea s.r.l., Carpi, Italy). This complete ECT process has been described in detail elsewhere[11].

Statistical analysis

The data are presented as the means ± standard deviations, ranges, or proportions. A two-sided *t* test was used for numerical data comparisons, whereas the χ^2 test was used for categorical data comparisons. Disease-free survival was analyzed via Kaplan–Meier analysis and the log-rank test. The disease-free period was defined as the interval from the first ECT to the recurrence of a disease. The patients were followed as late as February 2024. Statistical analyses were performed with SPSS version 27 (SPSS Inc., Chicago, Illinois, USA). Differences were deemed statistically significant at p values less than 0.05.

Results

Patient and tumor characteristics

During the study period, 116 elderly patients over the age of 65 were treated with ECT and intravenous bleomycin for a total of 257 histologically proven BCCs. The mean age of all patients at the time of treatment was 82.3 ± 6.1 years (range, 65.6–96.6). There was a preponderance of males among the treated patients, with a male-to-female ratio of 2.5:1.

The majority of patients (n = 175, 68.1%) were treated with a reduced dose of bleomycin, whereas the remaining 31.9% (n = 82) received the standard dose. There were no differences in the baseline demographic data between the analyzed groups (Table 1). The largest tumor diameter in patients treated with a standard dose ranged from 2 to 100 mm, whereas within the reduced dose group, the largest diameter ranged from 3 to 65 mm. Approximately two-thirds of the treated tumors in each group were naïve. More detailed comparison of patient and tumor characteristics between the groups is provided in Table 1.

Disease-free survival analysis

The mean follow-up times for the patients who received standard and reduced doses were 23.6 ± 22.5 months (range: 0–106; median: 12) and 17.6 ± 14.5 months (range: 1–77; median: 13), respectively. The comparison of disease-free survival showed a marginal difference between the reduced- and standard-dose groups (Fig. 1a; $p = 0.041$, log-rank test).

A more detailed subgroup comparison of naïve and non-naïve tumors was conducted. There were no differences in the recurrence rates when the standard and reduced dose groups were independently compared (Table 2). Additionally, subgroup analysis of disease-free survival between the naïve (Fig. 1b) and non-naïve (Fig. 1c) tumors showed no significant differences between the standard- and reduced-dose groups.

BCCs within the reduced dose group recurred in 40 (22.8%) ECT-treated tumors, whereas BCCs recurred in 11 (13.4%) of those patients treated with the standard dose. The median time until the recurrence of BCC within the reduced-dose group was 9 months (range: 2–69). Twenty-four of those recurrences (60.0%) were noted within the first year after ECT. Nine recurrent tumors from the reduced group (five of them naïve), with the largest tumor diameter of 20.6 ± 12.6 mm, were further treated with a normal dosage of bleomycin (i.e., salvage ECT). The disease recurred in none of those patients. The mean follow-up after salvage ECT was 9.8 ± 6.2 months (range: 3–25; median: 8). Similarly, 54.5% of the recurrences (n = 6) in the standard group occurred within the first 12 months following initial treatment. The median time until recurrence in this group was 6 months (range: 2–47).

Discussion

In this retrospective study, the long-term outcomes of BCCs treated with ECT and a reduced dosage of bleomycin were assessed and compared with patients treated with the standard bleomycin dosage. The recurrence rates between the two cohorts were comparable, regardless of whether the tumors were treatment naïve or previously treated. There was a marginal difference in disease-free survival, with patients who received the standard dose exhibiting marginally better disease-free survival. Notably, in cases of recurrence, the application of the standard bleomycin dosage as a salvage treatment proved to be particularly effective.

The rationale for proposing a reduction in the bleomycin dosage was grounded in a prior pharmacokinetic study involving older patients, which demonstrated a slower monophasic elimination of the drug compared to biphasic elimination in the adult population[10]. Several factors likely contribute to elevated bleomycin concentrations in the bloodstream, including a reduced volume of distribution caused by age-related changes in body composition, such as decreased water content and lean muscle mass, as well as impaired renal function[12]. While a higher local concentration of bleomycin may be beneficial because of the enhanced inflammatory response, it is also associated with extensive necrosis, leading to ulceration and a prolonged healing process. These findings were further elucidated in a smaller cohort of nonmelanoma skin cancer patients treated with ECT with standard and reduced doses (10,000 IU/m^2) of bleomycin[11]. The patients treated with the reduced dose exhibited less pronounced skin ulcerations, crusting, and scarring. Since more than two-thirds of BCCs occur in exposed areas of the head and neck, minimally invasive treatment option is of major importance[21,22].

Given that BCCs do not necessarily recur even after incomplete excision, it has been speculated that a response mediated by the immune system during wound healing may contribute to tumor regression[23,24]. In a randomized control study, Clover et al. compared standard-dose ECT with surgery and reported that ECT was an effective and durable treatment for BCC and was particularly convenient in patients who were not suitable or unwilling to undergo a standard surgical procedure[5]. The reported range of complete response rates with standard intravenous doses of bleomycin varies across studies and generally falls between 67 and

	Standard dose (n, %)	Reduced dose (n, %)	*P* value
No. patients	32 (27.6)	84 (72.4)	†
Male gender	16 (50.0)	56 (66.7)	0.098
Age [years][1]	80.7 ± 7.8	83.0 ± 5.8	0.086
Treated tumors	82 (31.9)	175 (68.1)	†
LTD [mm][1]	23.9 ± 15.9	21.2 ± 10.8	0.078
Naïve tumors	54 (65.9)	129 (73.7)	0.194
Previously treated tumours[2]	28 (34.1)	46 (26.3)	

Table 1. Demographic characteristics of the patients based on the bleomycin dose. Data are presented as absolute values with proportions unless otherwise specified. Statistical analysis was performed via the $\chi 2$ test or two-sided *t* test, as appropriate. ns—nonsignificant, LTD—largest tumor diameter, †—not analyzed. [1]presented as the mean with standard deviation ($\bar{x} \pm SD$), [2]previously treated either by cryosurgery, surgical excision, radiotherapy, and/or immunomodulators.

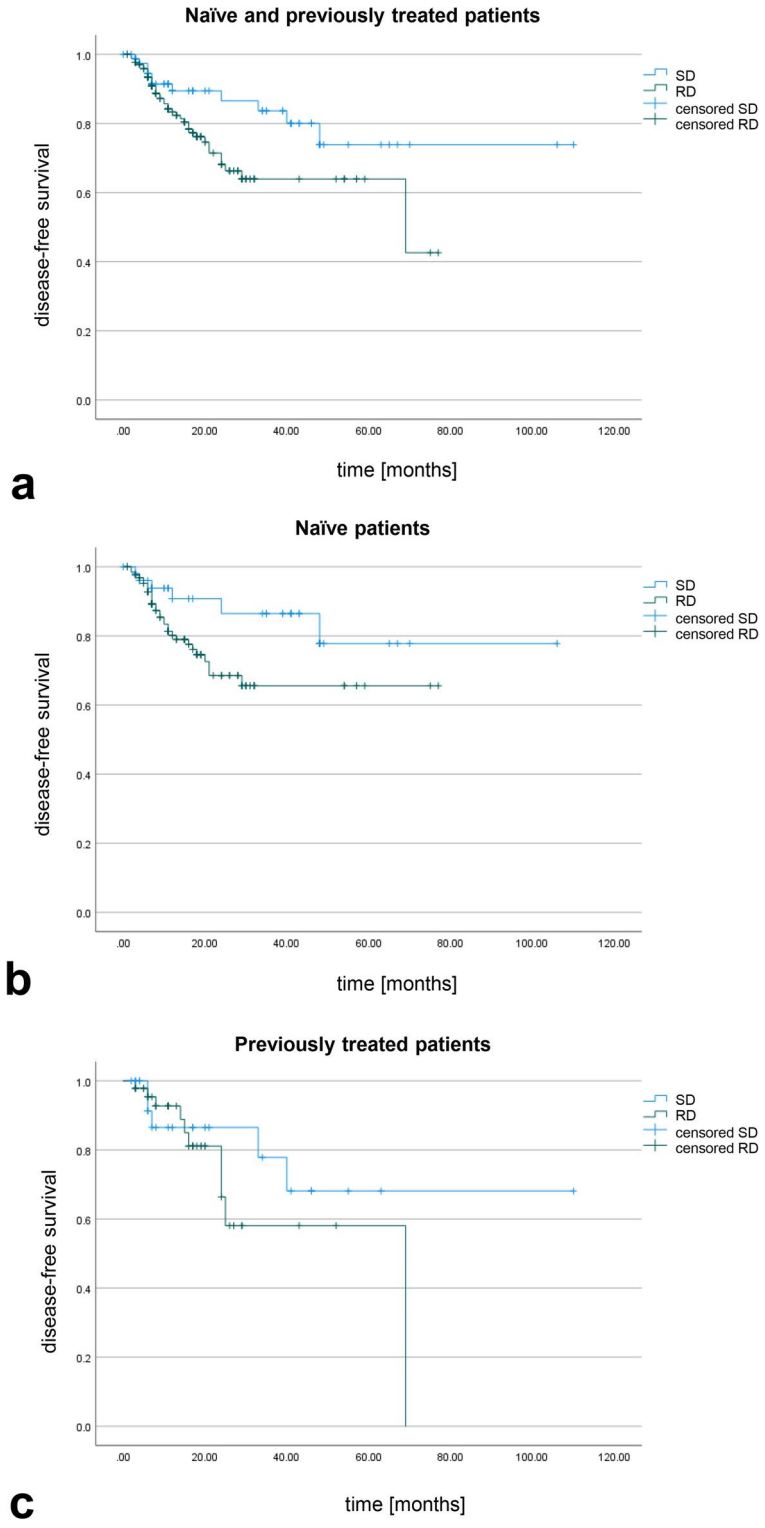

Fig. 1. Kaplan–Meier analysis of disease-free survival. Panel **a** depicts a disease-free survival comparison of the patients who received standard and reduced doses of bleomycin, regardless of the previous treatment strategy ($p = 0.041$, log-rank test). In panel **b**, the disease-free survival of patients with naïve tumors who underwent electrochemotherapy with standard versus reduced doses is shown ($p = 0.064$, log-rank test). Panel **c** compares disease-free survival within the non-naïve tumor subgroup between the standard and the reduced-dose groups ($p = 0.338$, log-rank test). SD—standard dose, RD—reduced dose.

		Standard dose	Reduced dose	*P* value
Naïve	Recurrence	6	30	0.059
	No recurrence	48	99	
Previously treated[1]	Recurrence	5	10	0.687
	No recurrence	23	36	
Naïve and previously treated[1]	Recurrence	11	40	0.077
	No recurrence	71	135	

Table 2. Tumor recurrence based on naïve or non-naïve grouping. The data are presented as absolute values. Statistical analysis was performed via the χ^2 test. [1]previously treated either by cryosurgery, surgical excision, radiotherapy, and/or immunomodulators.

98%[10,11,25,26]. The response rate in these studies was typically evaluated 2 or 3 months after the procedure. Some authors reported marginally better outcomes with fewer recurrences than patients in this study; however, these differences could be attributed to the relatively low number of assessed patients and shorter evaluation period[26].

Our study focused primarily on long-term outcomes rather than on evaluating safety and complications. The findings indicate that long-term disease-free survival was marginally better in the control group. Recurrences within the first year were comparable across groups; however, a greater number of recurrences were observed in subsequent months at the lower dosage of bleomycin, which is expected due to the extremely high mutational burden of BCCs[27]. As the antitumor effects of the ECT are partially driven by an immune response initiated by immunogenic cell death and increased tumor antigen expression, a reduced dose of bleomycin may weaken the local immune response, potentially leading to a higher recurrence rate of BCC[7]. The patients receiving the reduced dose yielded nearly equivalent long-term results within the initial months following the treatment. Given that many patients have already surpassed their expected lifespan at the time of BCC presentation, maintaining their overall quality of life is imperative. In the event of recurrence within the reduced-dose group, administering salvage ECT with a standard dose of bleomycin was highly effective in treating BCC. Contrarily, a reduced bleomycin dose may be less suitable for patients with a longer life expectancy who are more prone of being lost to follow-up.

In another retrospective analysis, Rotunno et al.[17] reported that ECT de-escalated doses of bleomycin, even up to half (7500–13,500 IU/m^2), can be employed on a wide range of nonresectable cutaneous malignancies. This approach is particularly convenient for patients who are candidates for multiple cycles of ECT or who have impaired renal function. More importantly, the authors highlighted that reduced doses did not compromise the antitumor activity of bleomycin, a finding that aligns with our results. Furthermore, as the cumulative dose of bleomycin must not exceed 400,000 IU[9], reducing the individual dose permits the possibility of administering multiple treatment courses if needed. These two studies support the idea that tailored dosing could enhance patient outcomes by balancing efficacy with the need to reduce potential drug-related toxicity, particularly in patients with more comorbidities and poor performance status[28]. Conversely, in patients with severe chronic kidney disease, the benefit of a reduced bleomycin dose may be outweighed by the need for additional treatment sessions, ultimately resulting in a higher cumulative bleomycin dose. Therefore, patient selection should be considered cautiously, taking patients comorbidities into the account.

This study had several limitations, with the primary limitation being its retrospective nature. To achieve a more unbiased assessment of lower bleomycin doses on BCC, randomized, prospective, and multicenter studies are warranted. Another limitation of this study is the non-standardized follow-up protocol, which is dependent on several factors, such as patient compliance, the extent of the disease, and comorbidities. The third limitation is the diverse groups of BCC tumors and their locations within both groups. Although the malignancies were histologically confirmed as BCC, the specific histopathological types (nodular, superficial, infiltrative, or morpheaform) or site of tumor presentation, which are strongly related to recurrence[29], were not considered in the analysis.

In conclusion, ECT with a reduced dose of bleomycin is a viable treatment option for elderly patients with BCC, offering a recurrence rate comparable to the standard dose, particularly within the first year after treatment. The selection of patients eligible for a reduced dose should consider their expectations, comorbidities, and life expectancy. Consequently, elderly patients with a limited expected lifespan may be more appropriate candidates, whereas those with a longer life expectancy, who are more likely to be lost during follow-up, may be less suitable.

Data availability

Raw data is available on request from the corresponding authors.

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Author contributions

A.G. and G.S. designed, conducted, and supervised this study. C.J. collected the data and helped with first draft writing. S.K., M.O., and M.C. participated with manuscript writing and critical analysis of data. L.P. performed statistical analysis and prepared the first manuscript draft. All authors helped with manuscript writing, reviewed, and approved the final version of manuscript.

Declarations

Ethical approval

The protocol was approved by the National Medical Ethics Committee of the Republic of Slovenia (Permit No. 182/02/14, 0120-132/2015-2). The procedures were conducted in accordance with national guidelines and per the Helsinki Declaration, with a written informed consent obtained from each included patient.

Competing interest

The authors have no conflicts of interest to declare.

Additional information

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